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NOTICE

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6 copies January 10, 1929

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CARCINOMA OF THE HEAD OF THE PANCREAS*

BY IRVING J. WALKER, M.D., F.A.C.S.†

THE following study is based upon a series of fifteen consecutive cases of carcinoma of the head of the pancreas. These cases were treated during the last twenty-two months, thirteen in the Boston City Hospital and two in other hospitals. All fifteen were operated upon.

The diagnosis, made from symptoms, signs, and laboratory data, was confirmed as accurately as possible by operative findings. In no case, however, was biopsy of the pancreas done because of the danger of subsequent hemorrhage or pancreatic fistula attendant with removing pancreatic tissue.

All of the cases showed a hard mass at the head of the pancreas, clinically more consistent with new growth than with chronic pancreatitis. In three cases it was possible to remove a portion of a metastatic gland for examination, which in each instance was found to be carcinoma.

In addition to the above series, four other cases operated upon with the preliminary diagnosis of carcinoma were found to be:

(1) common duct stone with chronic pancreatitis.
(2) hemochromatosis with hepatitis.
(3) cirrhosis of the liver of the atrophic type.
(4) carcinoma of the gall-bladder with metastases.

In these nineteen cases of suspected carcinoma of the head of the pancreas there was, therefore, an error of 21.1% in the preoperative diagnosis.

Carcinoma of the pancreas is not a common disease. Mirraillié[1] collected 31 cases in 41,949 patients. At this hospital there have been 27 cases in 6900 autopsies. White[2] found 31 cases in 6708 postmortem records.

According to Ewing, there are two main types of carcinoma of the pancreas:

(1) the adeno-carcinoma arising from the ducts and commonly found at the head of the pancreas.

(2) the carcinoma simplex, which is usually scirrhus, arising from the parenchyma and which is a diffuse type.

*From the Harvard Surgical Teaching Service of Boston City Hospital.
Read before the Clinical Meeting of the American College of Physicians at Boston City Hospital on April 12, 1929.

†For record and address of author see "This Week's Issue," page 339.

Considering the approximate duration of the disease as being from the onset of symptoms to the time of seeking medical advice, which was four and one-half months, together with the fact that metastases were found in only three cases, one would be justified from our study in inferring that carcinoma of the head of the pancreas does not tend to metastasize as early as does carcinoma in some other locations of the body. In the three instances where metastases were present, two were found to be in the region of the portal vein, and one in the liver.

In this series, neither gall-stones nor pancreatic calculi were found in a single instance, thereby eliminating these factors as causative agents of carcinoma.

The pathological findings of carcinoma in association with chronic pancreatitis point to the latter as a possible etiological factor.

Glycosuria was present in one of these fifteen cases. This was known to have existed for several years previously. Futcher[3] found it in 3 of 31 cases, and Miraillié in 31% of 52 cases. That glycosuria is not more frequent in carcinoma of the pancreas is accounted for by Opie[4] as being due to the fact that "the Islands of Langerhans persist within the stroma of the new growth until destruction of the gland is far advanced." Our series being such that the disease was confined to the head of the pancreas would explain the absence, with one exception, of glycosuria.

AGE

As in the case of carcinoma in general, the incidence of carcinoma of the pancreas increases with age. Speed[5], in 52 cases, found the average age to be fifty-seven. The average age in our series was fifty-eight. In Futcher's study, the oldest was seventy-five and the youngest thirty-four. Herringham[6], reporting from the records of St. Bartholomew's Hospital, cites a case in an infant of two years.

SEX

Futcher reports 22 males and 9 females; Speed 36 males and 16 females; and our series 9 males and 6 females with the disease. Most of our cases occurred in individuals who were, or had been inclined to be, obese.

DURATION OF DISEASE

The duration of the disease, dating from the earliest symptoms, which were usually some form of epigastric discomfort often termed "indigestion", was four and one-half months.

SYMPTOMS

The following symptoms are considered in order of the frequency in this series:

JAUNDICE

Jaundice was present in all fifteen, explained by the fact that the disease originated primarily in the head of the pancreas and hence involved the common duct relatively early in the course. The average duration of the jaundice was four and one-half weeks. Speed found jaundice in 80%, and Cameron[7] in 70% of cases. Futcher noted its presence in 23 cases, its absence in 6, and not mentioned in 2. However, in these series there were cases in which the head of the pancreas was not involved.

In our cases, the degree of jaundice, measured by the icterus index, varied from 18 to 60 with an average of 34.

PRURITUS

As in most cases of obstructive jaundice, our group showed pruritus to be a distressing symptom. It was present in all fifteen.

DIGESTIVE DISTURBANCE

All of our patients complained of some variety of digestive disturbance, which was generally referred to the stomach. This included belching of gas, epigastric distress or fullness, and in five instances intermittent vomiting. However, there was nothing of diagnostic aid in the interpretation of these digestive disturbances which would help in establishing the positive diagnosis of carcinoma of the pancreas.

PAIN

Pain was present in ten of the fifteen cases. Futcher reports pain in 25 of 31 individuals, and states that it was the most prevalent symptom in his study. Most of our cases located the pain in the epigastric region or just to the right of the midline. It was generally described as dull and intermittent. Three also referred the pain to the back as well as to the epigastrium. The epigastric pain may be attributed to pressure of the tumor mass on the coeliac plexus.

Three of the ten stated that the pain had been colicky early in the course of the jaundice. Speed noted this and interpreted the colicky character as being due to the backing up of bile in the gall-bladder. Einhorn[8] attributed this to an increase in muscular activity or increase of peristalsis following the intake of food.

LOSS OF WEIGHT

Twelve of our cases stated that there had been loss of weight. In one there was no loss, and in two this could not be determined. The average loss of weight in twelve individuals was 18 pounds. Speed found that loss of weight was the most constant symptom in his series.

Loss of weight can be accounted for by anorexia and interference with the flow of pancreatic secretion.

Coincident with the shutting off of the flow of pancreatic secretions one would expect some degree of acute pancreatitis. In reality this does not occur in experimental work where the pancreatic ducts are ligated, or in humans where the ducts are occluded by new growth.

URINE AND STOOLS

All fifteen noted the urine as being dark. Thirteen observed clay colored stools. Two made no observation as regards this.

CHILLS AND FEVER

None of our cases gave a history of chills or fever. During the period of observation before operation, it was not unusual to find an afternoon temperature rising to 99.4.

PHYSICAL AND LABORATORY FINDINGS

The degree of jaundice, as measured by the icterus index, varied from 18 to 60, averaging 34.

A qualitative van den Bergh test was done in twelve, with a biphasic reaction in each instance.

None of our cases showed enlargement of the liver. Speed found it enlarged in 12 of 31 cases. With one exception this enlargement was due to metastases.

In none of our series was there enough fluid found in the peritoneal cavity to be deemed pathological. Ascites was found in 13 of 113 cases collected by Miraillié, 4 in 31 by Futcher, and in 20% by Speed. We account for the absence of ascites in our group by the small number of cases showing metastases, and because in the three cases where metastases were present they were not of sufficient size, or their location was not such as to cause obstruction to the portal vein.

On physical examination, a tumor, later proven to be the pancreas, was found by us in seven individuals.

On examination, the gall-bladder was found enlarged in ten instances. However, at operation all fifteen showed a distended gall-bladder. The discrepancy in preoperative and operative findings as regards the enlargement of the gall-bladder is accounted for by the obesity of the abdomen in those cases where the enlargement was not found on physical examination.

Examination of the stomach contents was made in nine cases. Eight of these showed an

acidity within normal limits, and one a slight subacidity. From this observation we are led to believe that one should not be influenced against the diagnosis of carcinoma of the pancreas by the findings of a normal or even increased acidity of the stomach contents.

Clay colored stools were observed in each of the fifteen cases.

Blood counts, smears, and determination of the hemoglobin revealed nothing of significance other than an occasional mild secondary anemia. The average of the blood sugar determination after fasting was 91 mg. per 100 c. c.

The average bleeding time was four minutes, and the coagulation time thirteen minutes before the use of calcium.

In none of these cases was there a history of hemorrhage or any instance of petechiae. Speed notes a history of bleeding in 11 of 52 cases, but does not mention petechiae.

X-ray of the gastro-intestinal tract failed to be of any aid in revealing pathology of the pancreas. With one exception, the Graham test was not used, since we believed that the gall-bladder would not fill. We also hesitated to use this method because of the additional burden of excretion of the dye to possible damaged liver cells.

PREOPERATIVE PREPARATION

Our treatment before operation was based on the presumption that some degree of liver dysfunction existed in each case. As a consequence, the diet was regulated, limiting the protein and fat intake, but increasing the carbohydrates.

On the day previous to operation, glucose was given by rectum and on the morning of operation intravenous glucose was added. The fluid intake was encouraged.

No case was operated on until the coagulation time was brought down to nine minutes or less by the use of calcium. Calcium chloride, 5 c. c. of a 10% solution, was given daily for three doses, including the day of operation, to every patient, regardless of whether the coagulation time was normal or not. Transfusion was not done before operating in this series.

We showed no preference in choosing the anesthetic, using local, spinal, or a general anesthetic as seemed to fit the case, taking into consideration the temperament, age, and conditions of the renal, respiratory, and circulatory systems.

OPERATION

Cholecystogastrostomy by the suture method was done in all fifteen. Our choice of cholecystogastrostomy rather than cholecystoduodenostomy was based on the fact that the former procedure seemed technically the less difficult. We realize that cholecystoduodenostomy is physiologically more rational.

Endeavor was made to have the stoma approximately 2 c. m. in diameter. The opening in the stomach was placed just proximal to the plyorus. Tension in the suture line was carefully avoided.

The Murphy button, as advocated by Walters, may be preferable to anastomosis by suture, since it should better control bleeding and assure a patent stoma from the start. Walters states that the increase in jaundice sometimes noticed after anastomosis by suture may be due to oedema about the stoma temporarily blocking the latter. We noticed this temporary increase in jaundice in three patients.

The under surface of the liver was in each instance drained with rubber tissue through a stab incision. A discharge of bile, the result of leakage at the stoma, occurred in four cases.

POSTOPERATIVE

The tendency to postoperative bleeding occurred in two cases. In one of these there was unquestionably bleeding from the stoma. This ceased following transfusion. In the second case, a considerable hematoma developed. This was controlled by the use of calcium and finally disappeared.

In eight cases there was an accumulation of large amounts of bile in the stomach, which necessitated lavage.

There was no mortality during the hospital stay of these patients.

Gain in weight varying from five to sixteen pounds within two and one-half months occurred in ten cases. In three of the others there was no gain or loss of weight in this time. The remaining two showed loss of weight.

Most of the cases showed a slight improvement in appetite. The digestive disturbances did not show any particular improvement. In most, this complaint grew gradually more pronounced. The same fact was noted regarding the character and severity of the pain.

In each case, pruritus disappeared not to return. The period of disappearance varied from three to five days.

Clinically the jaundice disappeared in each case in from four to six weeks. The cases have not been studied since operation as regards the icterus index. Possibly latent jaundice existed in some.

In six, gastric studies were made with barium to determine whether or not there was a reflux of stomach contents into the gall-bladder. Three showed a distinct "budding" as if some of the barium had entered the gall-bladder. However, none of the cases have demonstrated any symptoms of a marked ascending biliary tract infection.

Nine patients have died as a result of the disease. These showed an average duration of life from the onset of the disease of one year and two months. The remaining six are at present in varying degrees of health, most with very little discomfort.

SUMMARY

The percentage of error in the diagnosis of carcinoma of the head of the pancreas is still such that one is justified in advising exploration in doubtful cases of obstructive jaundice.

Cholecystogastrostomy in properly prepared patients is not a difficult or serious operation.

Relief of certain symptoms, especially pruritus, justifies the operation, as a palliative measure, in cases of carcinoma of the head of the pancreas.

REFERENCES

1 Miraillié: Gaz. des. hôp., 66:889, 1893.
2 White, W. H.: Guy's Hosp. Rep., 54:17, 1897.
3 Futcher, T. B.: Carcinoma of Pancreas, Tr. Assoc. Am. Phys., 34:284, 1919.
4 Opie, E. L.: Diseases of the Pancreas, J. B. Lippincott Co., Phila., Ed. 2, 1910.
5 Speed, K.: Carcinoma of the Pancreas. Am. Jour. Med. Sc., 160:1, 1920.
6 Herringham: Primary Carcinoma of Pancreas, St. Bartholomew's Hosp. Rep., 30:5-15, 1894.
7 Cameron, G.: Carcinoma of the Pancreas, M. J. Australia, I:414-418, April 26, 1924.
8 Einhorn, M.: Pancreatic Tumors, Am. J. M. Sc., 172:796, 1926.

RECENT ADVANCES IN THE BIOLOGY OF CANCER*

BY HENRY JACKSON, JR., M.D.†

INTRODUCTION

IT is impossible in a short article to cover even in a cursory manner all of the numerous studies that have been made in the subject of malignant disease during the past twenty years. In certain fields more striking advances have been made, or more interesting theories raised, and it is to these that we shall confine our attention. The problem of heredity always is of great concern to both physician and patient. The treatment of malignant disease and particularly that which has recently been advocated by Blair Bell of Liverpool, is of vital interest. A notable advance has been made in the understanding of the fundamental chemical process of malignancy by Warburg and his co-workers, and has been confirmed by others. Gye of London has again raised the question as to whether malignant disease may not be of parasitic origin, and his work at present commands much attention. The relation of vitamins to cancer has been brought forward in recent years and much interesting work has been done along this line.

HEREDITY AND CANCER

The existence of cancer families has often been brought forward as evidence of the inheritance of neoplastic disease, but we must sharply distinguish, in such investigations, between the congenital tumors, such as retinal glioma, neurofibroma, and multiple enchondroma, and true heredity tendencies. The congenital tumors, are, of course, conditioned by intrauterine conditions, whereas when true hereditary factors are involved these factors can be submerged completely and carried on through several generations without frank emergence. Thus, the hereditary tendency to albinism in mice may be held back without appearance for 25 or more generations; and it will remain submerged beneath the dominant character until the appropriate hybrids are again bred together. On the contrary, intrauterine influences determine the congenital tumor and no submerged tendency is carried along by an otherwise healthy animal. As Ewing has pointed out, the rare occurrence of a family with much cancer in it is, perhaps, an argument against the true inheritability of cancer by and large. Furthermore, statistics in such a matter are always treacherous, and the study of cancer families has added but little to our knowledge of whether cancer is hereditary or not.

The statistical study of inheritance of cancer was begun by Paget[1] who found cancer in 23.6 per cent. of the relatives of 254 cancerous patients, as against 18.3 per cent. in non-cancerous patients. Other authors[2, 3, 4, 5, 6] find a far smaller percentage of inheritance in their series, averaging only 7.1 per cent. Weinberg[7], from the clinic at Stuttgart, found no evidence of heredity in his figures. Little[8], on analysis of the statistical data obtained in the family history records of the Eugenics Office, Carnegie Institution, found, first, that in families whose fathers were cancerous and whose mothers were normal, there were 1717 total non-cancerous individuals and 24 ±3.27 cancerous, an excess of the observed over the expected of 22.1, and he calculates that the odds against this excess being due to chance alone would be more than 100,000 to 1. Similarly, when the immediate progeny of cancerous mothers and non-cancerous fathers were analyzed, it was found that 1030 were non-cancerous and 39 ±4.13 were cancerous, an excess of 36.22 over the expected number of cancerous individuals, 2.78 in this case. Finally, an examination of the blood relations of cancerous individuals, as against those of non-cancerous individuals, showed, again, an excess of observed over expected cancerous individuals. He finds that in the general population 1.23 ±0.03 per cent. are cancerous, whereas 2.32 ±0.22 per cent. of the sibs of cancerous individuals have malignant disease. Little says,

"From both these sources of data it may be concluded that a tendency to the formation of cancer is clearly inherited. The influence of inheritance is shown by the occurrence of a marked excess of 'cancerous' individuals over

*Thorndike Memorial Laboratory, Boston City Hospital.
This paper is an abridgment and revision of a more complete article appearing in Medicine, Vol. 7, Aug., 1928.
†For record and address of author see "This Week's Issue," page 339.

the rate of the general population, in (1) the sibs of 'cancerous' individuals, (2) the progeny of 'cancerous' mothers by 'non-cancerous' fathers, (3) the progeny of 'non-cancerous' mothers by 'cancerous' fathers. The fact of inheritance is clear but the type of inheritance needs further investigation."

In any statistical study of the inheritance of cancer, one must remember, however, that the error in diagnosis is large, probably as high as 25 per cent., that the age span of the various individuals in the families may differ, and that supposedly non-cancerous controls, may, of course, subsequently develop cancer.

The early work of Bashford and Murray[9], Loeb[10] and Tyzzer[11, 12, 13] all showed that in mice there was an hereditary tendency to cancer. The most interesting experimental work has come from Maud Slye[14, 15, 16, 17, 18]. She has worked exclusively with spontaneous mouse tumors. Cancer, she believes, is recessive to non-cancer, and the first hybrid generation never has shown it in all of her experience. When a non-cancer strain has once been extracted, spontaneous neoplasms never have occurred again in her series. With a double cancerous parentage, she believes that the offspring will be 100 per cent. cancerous. With a single cancerous parent, the offspring will be heterozygous to cancer, in other words, they will transmit, but will not necessarily develop, cancer; and these heterozygous individuals will yield non-cancerous, heterozygous, or cancerous individuals in approximately the proportion 1 to 2 to 1. She further concludes that double non-cancerous parentage means that cancer, provided the race remains homogeneous, will never appear again. She points out, that in her series of animals, organ specificity is marked and she believes that liver tumor begets, in the offspring, liver tumor and that stomach tumor gives rise to stomach tumor in the future generations. Immunity to cancer, as a corollary to her conclusions, should be, of course, a dominant; and, although for a long time she apparently did not believe that there was any factor concerned other than the simple mendelian recessive, she later came to the conclusion that two factors might be necessary for the production of cancer, first, an inherited local susceptibility to the disease, and, second, an irritation of the right kind and in the right degree[26].

She says[23]—

"The fact that various types of irritation play an important part in the causation of cancer in susceptible individuals is one of the best basic arguments for defining cancer as an abnormal regeneration process. This regeneration after trauma is apparently abnormal in these cancer-susceptible subjects because of the lack of a differentiating mechanism in the tissues. It seems to be this lack of a differentiating mechanism in the susceptible tissues that is the hereditary element in cancer susceptibility. That is, the type of local response made to a given type of irritation is determined by heredity whatever the type of that irritation may be." She objects to arguments based on the use of transplantable tumors, and she believes that transplantable tumors are the exact opposite, in their genetic relations, to spontaneous cancer, for in the latter the tendency of the assaulted tissues is to regenerate abnormally in an uncontrolled and undifferentiated manner. She sees, therefore, no contradiction in the fact that, whereas she has found cancer to be a simple mendelian recessive most workers in the field of *grafted* tumors find that these behave as a dominant, though not, in most cases, as a simple dominant.

To Slye's work Cockayne[28] objects (in so far as the mammary carcinoma is concerned) that in most cases "she has used in generation after generation a mouse with carcinoma of the mammary gland as one parent, and although she proves, in this way, beyond doubt, that the tendency to cancer is inherited, she does not prove that it is inherited as a recessive. She regards these crosses as crosses between a mouse homozygous for, and one heterozygous for, mammary carcinoma, but the same result would be obtained if the tendency to carcinoma were dominant, and the cross were between a mouse heterozygous for the condition and one homozygous for the normal." Cockayne concludes that "She (Slye) has been dealing with three hereditary disorders, each one due to a separate unit character and consequently inherited independently". These disorders (according to Cockayne) are "adenomatosis of the lung and of the liver, which are probably recessive, and adenomatosis of the mammary gland, which is probably dominant. Malignant disease develops in a comparatively small proportion of the first two, and in a very high proportion of the last of these. . . In the case of tumors of mice, Slye produces no complete proof that they are inherited, though her pedigrees suggest that some behave as mendelian recessives and others as dominants."

Wells[123], on the other hand, agrees in general with Slye's results; but he is not entirely convinced that these figures and theories can be transferred to the human race.

Little says, "In the interpretation of her data, there is room for grave disagreement in her conclusion that cancer behaves as a simple mendelian recessive. Even admitting the difficulty introduced by occurrence of cancer at an advanced age in the lifetime of an individual and the limitation of the most common class of tumors due to sex (mammary carcinoma), it is still evident that a simple type of mendelian inheritance does not fit the observed facts sufficiently well. Furthermore, the fact that certain families of mice show such a higher incidence of neoplasms located in a particular locality indicates that subsidiary or modifying factors are influencing the situation and in all

probability the occurrence of neoplastic growths." Little agrees that it has been proved beyond question that heredity factors play an important part in the determining of the incidence of cancer in mice but he feels that though the fact of inheritance is undoubtedly established, the method of inheritance is not yet determined. He[30] expresses the "hope that great caution will be exercised by those reading the interpretations of these two investigators (Slye and Wells) before accepting their conclusions that cancer is a simple Mendelian recessive." He believes that Lynch is correct in her contention that mammary cancer in mice behaves like a Mendelian dominant—a conclusion directly opposite to that of Slye. It is possible and permissible to argue the existence of hereditary tendencies of cancer in man from the existence of such tendencies in other animals. Similar arguments have been shown to apply in such abnormalities as albinism and color of the eyes, but Little emphasizes the extremely complicated biological nature of cancer, occurring as it does in middle life or old age, at a point very far removed from the carriers of the elementary heredity tendencies; and, the opportunity for the effects of internal environment to become excessively complicated and amplified are, of course, obvious. As regards cancer inheritance in man, he points out that one is faced with inadequate methods of observation, diagnosing and recording, the magnified effects of environment due to the long life-cycle, small numbers of young, and a deliberate system of out-breeding which confuses the situation. All these factors make the study of inheritance of cancer in man very difficult.

The more recent work of Murray[31] shows that environmental changes do indeed alter the tumor incidence in mice. He found that enforced non-breeding "delays very markedly the age of tumor incidence and may even inhibit entirely the development of cancer in mice which would have had a high incidence of tumor appearance had they lived a normal sexual life." Furthermore, the complete absence of ovarian secretion (castration) was found to have much the same effect on cancer incidence as did enforced non-breeding. Once more, from these data it would appear that *factors other than heredity* have a marked influence on tumor incidence.

In summary, it seems fair to say, as Little has said, that the fact of inheritance in animals has been definitely proved, but that even here we are not positive of the exact mechanism of the inheritance. The transferal of these data to man, while permissible in part, becomes so complicated by such multiple factors as age span, and out-breeding that it is very difficult, if not impossible, to say what influence, if any, heredity has in cancer in man.

THE PARASITIC THEORY OF CANCER

The parasitic theory of the origin of malignant disease has been brought up many times in the past. It has been shown without doubt by Fibiger[32] that, in animals, cancer of the stomach may develop about encysted spiroptera. Similar observations have been made by Bullock and Curtis[33]. In these instances, however, we are dealing with a chronic irritation factor and not with any specific organism that might be of etiological importance in human cancer. Numerous authors, more recently Blumenthal[34, 35] and Nuzum[36, 37] have claimed to have isolated from animal and human cancer organisms with which they were able to reproduce malignant disease of a similar sort in experimental animals. Their work, however, has not been confirmed by others.

More recently the work of Gye[38, 39, 40, 41] has attracted much interest. Gye's theory, in brief, holds that all tumors are caused by two factors, a non-specific filtrable virus, common to all tumors, and a specific chemical substance which renders certain tissues susceptible to the virus and enables the virus to produce the lesion. His work has been largely with the Rous chicken sarcoma.

In 1911 Rous[42] described a new sarcoma of fowls which could be propagated from chicken to chicken by a cell free filtrate, though it was found impossible to transfer it to mammals even by using living cells. Other filtrable tumors were subsequently[43] found by Rous, but all were specific for fowl, so that doubts have been raised as to whether the Rous sarcoma is, indeed a true tumor in the usual sense of the word, though it may be argued that it has all the usually accepted criteria of malignancy and that the mere fact of its filtrability should not militate against these facts. Rous, himself, was non-committal as to the nature of the "agent" by which the tumor was propagated. He hesitated to call it a virus, but he and his collaborators showed that it was destroyed by a temperature of 55°C. for fifteen minutes and by chloroform, toluene, and phenol.

Gye's experimental evidence, in brief, is as follows: The virus from the Rous chicken sarcoma is obtained by grinding the tumor, after excision under strict aseptic precautions, with sand. Saline is added and the suspension filtered through sand until clear. This process yields the so-called "sand filtrate", which is capable of infecting fowl in doses as small as 0.05 ml. The active agent, or virus, in this filtrate may be killed by various agents[44], but Gye originally[39] used a "few drops of chloroform". After such treatment the "sand filtrate" is usually innocuous, even in doses as large as 2.0 ml. If, on the other hand, a small piece of tumor tissue be incubated for from 2 to 7 days in modified Hartley's broth under anaerobic conditions, this so-called "primary culture" also becomes non-infectious. A combination, however, of "sand filtrate" and "primary culture", neither of which alone will, as a rule, react, results in a tumor. Gye's as-

sumption is that there are two factors—a living virus and an accessory chemical substance. In experimental tumors produced by the combination of these two factors the former is contained in the "primary culture" and the latter in the "sand filtrate". Since the virus can be furnished by small amounts of sub-cultures of tumor tissues in modified Hartley's broth as high as the fourth or fifth generation, the resulting dilution of the tumor would seem to be sufficiently great to rule out mere survival of the agent. And, since the virus factor may be obtained from rat tumor No. 9, Jensen rat sarcoma, mouse carcinoma No. 63 and human carcinoma, it is assumed that it is present in all malignant growths and, hence, non-specific. The accessory chemical substance, on the other hand, is specific and determines the type of tumor. Gye assumes that the "chloroform treated sand filtrate contains a labile chemical compound which in some way, as yet unknown, renders the cells susceptible to infection by the virus contained in the primary culture."

A second line of evidence is seen in the following. A suspension of tumor tissue, incubated anaerobically at 39°C. is spun down at a high rate of speed, the supernatant fluid is removed and the sediment thoroughly washed with saline. Neither the supernatant fluid nor the washed sediment will alone produce a sarcoma, but when they are combined a tumor results. These experiments show that in suspensions of tumor tissues there are two factors which are necessary to the production of tumor—the one is particulate and is, therefore, probably a virus; the other, being uninfluenced by spinning, is probably a chemical substance.

There are two points in relation to Gye's work which demand serious consideration. In the first place, he has been able to recover the specific chemical substance from only one type of tumor, namely, Rous chicken sarcoma, which may not be a true tumor in the usual sense of the word. Furthermore, as he reports occasional "takes" with the specific chemical factor only, in amounts which are comparable to those used in experiments on which his theory is based, the point as to whether the original infective agent of the "sand-filtrate" has been killed or not is debatable.

Many objections, aside from the choice of tumor, have been raised against Gye's theory. Murphy[45, 46] was able to reactivate the chloroform filtrates by embryonic and by normal tissue, and he concludes that there is no necessity for the assumption of a living virus derived from tumor tissue. Flu[47, 48] has come to the same conclusions. McKenzie and Illingsworth[49], however, were not able to reactivate with embryonic or normal tissue, and they believe that their work supports that of Gye in this particular respect. They were, however, unable to subculture the virus as Gye had done. They were able to replace the virus from Rous chicken sarcoma by an agent from mouse carcinoma No. 63, but not from mouse sarcoma No. 37. They further state, "We have not been able to produce the Rous sarcoma from subculture and 'specific factor' in any instance where the specific factor alone did not likewise bring about a growth". They believe that the " 'specific factor' is in reality nothing more than a suspension of attenuated virus which may or may not produce a tumor, depending on the fowl's susceptibility or resistance." Further observations on this point must be made before the objection can be considered entirely vitiating Gye's theory.

Harkins and others[50] have found that, if a large amount of chloroform be added to the virus, it will be killed entirely, and that a few drops, as recommended by Gye, failed to destroy the virus in 25 per cent. of the cases. In fact, these authors still obtained frequent "takes" even when using 2 per cent. chloroform. It should be noted, however, that Gye's "sand filtrate" must be absolutely clear if chloroform is to act in a consistent manner, and not all investigators have paid sufficient attention to this point.

Mueller[51] has studied the problem experimentally and concludes, "We have absolutely no indication of the necessity of two factors in the production of the Rous sarcoma. . . . Because of the conflicting nature of the results obtained by those who have undertaken to repeat the work, and on account of the difficulty of controlling all factors involved, we do not feel that it may be stated definitely that Gye's theory of the cause of cancer is wrong."

Baker and McIntosh[52] find marked variation in the infectivity of the filtrate from Rous sarcoma, and they show that this variability is due to those factors which control ferment action, especially the hydrogen ion concentration. They suggest that "the discrepancies between the results of different workers upon the Rous sarcoma, particularly in relation to Gye's work, can be accounted for by a lack of control of" these factors. Cutler[53], again, was unable to confirm Gye's work. He concludes that the susceptibility of the Rous tumor filtrate to chloroform varies to such an extent that proper standardization of this technic is not possible.

Further work must be done before this theory can be proved or disproved, and it is too early, at present, to give a final opinion. There is no doubt, however, that many new facts of importance and interest will come from the experiments, no matter what the actual outcome is.

Finally, it should be remembered that there are numerous theoretical objections to the parasitic theory of cancer. The incidence, course, age distribution, and anatomical character of the disease are against such an assumption. Ewing[54] says in part, "The anatomical and physiological characters of malignant tumors differ essentially from those of known infectious process. The metastases of tumors

reveal conditions wholly different from any phenomena observed in infectious diseases. There is no more impressive illustration of the difference between tumors and infectious granulomas, which they most nearly resemble, than the comparison of the fate of tumor emboli and emboli from a tuberculous focus. In the former case the tumor cells grow where they lodge, receiving only nutriment from the blood of the part; in the latter case the embolic cells die and the transported bacilli excite an inflammatory process in the adjacent tissues. . . . . Tumors arise in some instances from a single cell, in most instances from a narrowly circumscribed group of cells, and grow chiefly or exclusively from their own resources. Few writers have ventured to suggest that benign tumors can be of parasitic origin, and yet occasionally tumors which are otherwise indistinguishable from benign growths, as adenoma of the thyroid and leiomyoma, may exhibit all the characters of malignancy. Hopeless dilemmas arise when one attempts to conceive of all the necessary properties of the cancer parasite." And Ewing concludes, "It is impossible to regard as a valid hypothesis the conception of a specific group of parasites living in symbiosis with the cancer cell and stimulating its growth and nutrition. All the facts are reasonably explained by regarding the cancer parasite as the cancer cell."

ACCESSORY FOOD FACTORS AND CANCER

The relation of accessory food factors or vitamins to malignant disease very naturally has come to the attention of workers in this field in recent years. The most interesting investigation in this relation is that of Burrows[55, 56, 57, 58, 59, 60, 61, 62, 63]. He believes that the neoplastic changes which cells undergo are due to the environment in which these cells reside, rather than to any specific organism or specific changes in the cells themselves. Growth differentiation and function he regards as determined, not by the cells themselves, but by their immediate surroundings. The view that cancer cells are capable of independent growth under conditions other than those favorable for the growth of normal cells he believes to be false, though it is hard to reconcile this view with the fact that cancer cells can be cultivated for a long time outside the body and still retain their malignant properties. His early studies were made on tissue cultures and he believes that growth is contingent upon the gradual accumulation in this stagnant environment of a substance which he names the archusia. This archusia he believes is formed by the cells themselves. In low concentrations S_1 it has no effect on the surrounding cells. In medium concentrations S_2, it causes the cells to migrate into solid media. In high concentrations S_3 the proteins and fats are digested and the cells grow and divide by mitosis. In all higher concentrations S_4, the cells themselves are digested. Burrows also assumes the elaboration of a second substance, fat soluble, which he calls ergusia, which reduces surface tension and coagulates fibrin and so aids the cells in migrating to distant parts, but which in turn, retards the growth of cells, as "archusia" aids their growth. From these studies of tissue culture Burrows was led to believe[60] that cancer is due to a local crowding of cells and a relative reduction in the blood supply of the mass both of which factors tend to increase archusia.

His co-worker, Jorstad, points out[61] that coal tar and other liquid fat solvents produce cancer by drawing the cells together into a compact mass. Animal parasites, likewise, cause a dense mass of cells to accumulate and these suffuse their own archusia and thus produce a local condition favorable to the proliferation of cells already crowded together. Radium and x-ray disturb the vascular supply and increase the production of archusia. Burrows shows[55, 63] that a dense mass of cells destroys any neighboring less dense mass of cells, just as cancer destroys the normal tissues about itself.

He points out[62] that in tissue culture, cells grow only when they are crowded together, and that, if a stream of fresh serum be passed over the tissue culture, growth and function cease, because, as he believes, the serum soluble archusia is washed away. The content of this substance Burrows finds to be high in embryonic tissue[64], and he points out the parallel of this fact to the observation of Robertson[65] that the rate of growth of paramoecia is directly proportional to the number of individuals per unit volume of medium until the medium becomes charged with waste products above a certain concentration. In short, Burrows believes that two substances in the environment govern the growth and activity of all cells—first, the archusia, water soluble, which allows cells to grow, differentiate, and function, and second, ergusia, fat soluble, which acts as a restraining force upon the unlimited and chaotic increase of cells by themselves—and that cancer is due to any process which upsets the balance by causing a relative increase in the concentration of archusia.

So far Burrows contributes little over and above the large school of investigators which believes that cancer is due to an imbalance between a growth promoting and a growth retarding agent. He takes a material step forward, however, in his proposed identification of archusia with vitamin B and of ergusia with vitamin A. This ergusia, he believes, is a product of growth reaction and inhibits growth, not as a foreign toxic substance, but as any product of an incomplete reversible reaction may inhibit the reaction when added in excess to the reacting system. In support of this rather striking view that these substances are really vitamins he brings forward a certain amount of evidence.

In the first place, he finds that both vitamin

B and archusia are plentiful in embryonic tissue, and that both reach their maximum concentration in a chick of five days[59, 63], at which period the growth rate is at its fastest. This growth rate decreases as the embryos age and in a similar fashion the contents of both vitamin B and of archusia decrease[59, 67]. Extracts of cancer cells cause tissue cells to grow very rapidly at first and then to disintegrate. An analogous growth stimulus and later disintegration is brought about by extracts of five day embryo. He considers that he has shown[59, 67] that cancer tissue (Jensen sarcoma) is high in vitamin B, but his protocols do not appear to prove this with certainty and experiments conducted in this laboratory[68] indicate that carcinomatous tissue has no higher vitamin B content than normal non-active tissue. Burrows concludes, however[67]—

"While it is impossible to prove without working with pure products that the archusia (S) of the cell is vitamin B, there is no evidence from these experiments that it is otherwise. Our test for the archusia is the ability of a cellular exudate to stimulate activity in tissue cells. The highest stimulating extracts are obtained from the most actively growing cells—cancer, young embryos, and actively growing young cultures of bacteria. These have been found to have the greatest amount of vitamin B."

Burrows further regards the "fat soluble ergusia" as having the general properties of vitamin A[67]. He finds that the ergusia lost to cells can be replaced by vitamin A and from this and other lines of evidence he concludes that vitamin A is "present as the ergusia in the intercellular substances in higher animals and in their stored fat." Vitamin A (or ergusia) he regards as formed during the growth reaction of cells and he believes that it must "slow the growth reaction of the cell", as does the product of any essentially reversible reaction.

Burrows believes, in short, that cancer is merely the result of anything which locally removes vitamin A from the tissues or locally increases vitamin B. X-ray causes cancer, according to this theory, by increasing the local amount of vitamin B and Burrows shows that animals on a vitamin B free diet will live longer if small doses of x-ray are given them. Parasites produce cancer—when they do—by their liberation of large amounts of vitamin B. Tar produces malignant changes by locally depleting the tissues of vitamin A and Burrows shows that animals killed by tarring can be saved by feeding large amounts of vitamin A. Chronic irritation with scar tissue tends to produce cancer by reducing the blood supply and allowing the archusia, or vitamin B, to accumulate. Burrows substitutes stagnation for chronic irritation, just as Warburg with somewhat less enthusiasm substitutes anoxemia for chronic irritation.

The natural consequence of this theory is that one should be able to modify the course of malignant processes by vitamins or other accessory factors. Much work has been done on this aspect. Sugiura and Benedict[66] found that absence of vitamin B from the diet had no effect on the tumor growth in animals. Wyard[69] was unable to demonstrate any effect when vitamin A was absent. Lapidari[70], however, felt there were less tumor takes in transplantable chicken tumors when the diet contained no vitamin B; and Ludwig[71] saw no tumor takes out of 60 animals on a vitamin free diet, as against 57 takes out of 60 control on normal diets. Kramer[72] found that absence of vitamins neither hindered nor accelerated the growth of animal tumors, while an excess of vitamins made the tumors grow more rapidly. Fujimaki[73], feeding rats a diet containing no vitamin A, found, as others have done, that there was a hyperplasia of the epithelium of the stomach, which he interpreted as carcinoma. Wolbach[74, 75] has amplified this work and found similar results but is not prepared to call the change carcinomatous. Goldblatt[78] comes to essentially the same conclusions. Most attempts to alter the course of cancer by dietary means have consistently failed, but this does not necessarily imply that they always will.

THE CHEMISTRY OF MALIGNANT DISEASE

Ever since 1836 when Johannes Muller[77] sought to isolate a specific chemical substance from carcinomatous tissue the interest in the chemical make-up and chemical behavior of malignant disease has increased. Many able chemists have worked on the problem, and from time to time substances have been isolated which were said to be characteristic of new growth, but this has subsequently been shown not to be the case. A careful chemical examination of carcinomatous tissue fails to show any substance to which the properties of malignancy might be attributed[78, 79, 80].

The most interesting work of recent years in the chemistry of carcinoma has come from the laboratories of Warburg[81, 82] and his associates[83, 84, 85]. Warburg[86] in studying the gaseous metabolism of sea urchin eggs, noted, as others had done, that their oxygen consumption was very large, increasing six times at the moment of fertilization. Inasmuch as carcinoma is a rapidly growing tissue with some superficial resemblance to the embryonic state, Warburg studied the metabolism of the Flexner-Jobling carcinoma and found, much to his surprise, that living cancer cells did not use much oxygen; in fact, they used very little. In an effort to overcome what he believed to be a technical error, he added sugar to the fluid medium in which his experiments were being made, and there then developed the fact, which has since been substantiated, that carcinomatous cells destroy sugar with great rapidity, either under anerobic or aerobic conditions. It is on this general

fundamental thesis that Warburg and others have evolved a working classification of various tissues which marks off malignant disease as a type of growth differing on the one hand from normal adult tissue and on the other hand from rapidly growing embryonic tissue.

Inasmuch as the fundamental metabolic processes are an expression of the mode of life and growth of any tissue it is by the qualitative and quantitative estimation of these processes that we may hope to arrive at an understanding of just what cancer is and how it behaves. Myerhof[87] has shown that muscle in contracting derives its energy from the hydrolysis of sugar. Pasteur has shown that some organisms live anaerobically. We have, therefore, two large sources of energy (and hence life) in tissues; first, the aerobic combustion of glucose to carbon dioxide and water, and second, the anaerobic glycolysis of dextrose to lactic acid. It is the relative proportion of these two sources of energy of tissue with which Warburg had concerned himself.

Certain definite facts have been brought out. The anaerobic glycolysis of tumors and other actively growing tissues is far more rapid than that of less active normal adult tissue. Cancer tissue forms nearly 10 per cent. of its dry weight of lactic acid per hour and so produces 100 times as much as blood, 200 times as much as the resting frog muscle, and 8 times as much as a fully acting frog muscle.

The presence of available oxygen in the reacting medium depresses the glycolytic rate in all types of tissue, but it does so most markedly in the case of normal adult tissue, where aerobic glycolysis is practically wanting, and in the case of embryonic tissue. When, therefore, tissue is transferred from anaerobic to aerobic conditions, we find that, if the velocity of the splitting process is great and the respiration slight, a greater part of the glycolysis will still go on. If, on the contrary, oxidation is great in comparison to hydrolysis, then the latter will cease to a large extent in the presence of available oxygen. Yeast, with its low oxygen consumption, and cancer tissue, behave in the first way; muscle, with its great oxygen consumption, in the second. With muscle, transference into an oxygen-containing medium brings about a virtual cessation of hydrolysis. With yeast and with cancer cells, on the contrary, transference to an oxygen-containing medium has but little effect upon the magnitude of the glycolytic change, for the respiration of cancer tissue is too slight to influence materially its power to transform glucose into lactic acid. Under anaerobic conditions in benign tumors, the glycolysis is of the same order of magnitude as with malignant growths, and we have, therefore, an indication that there is no great fundamental difference between malignant and benign tumors; but, under aerobic conditions, the difference becomes marked, malignant tumors producing three or four times as much lactic acid as do benign tumors. Embryonic tissue, under anaerobic conditions, produces lactic acid in large amounts, in fact, as much as does tumor tissue, but as I have noted above, the consumption of oxygen is very large in embryonic tissue and, consequently, the transference to a medium containing available oxygen results in the almost complete disappearance of the hydrolytic change. The respiration of normally growing tissues again suffices to bring about a virtual disappearance of the glycolytic products. Now, if we calculate from observed figures the amount of energy obtained by the oxidative mechanism on the one hand and hydrolytic processes on the other, we find that nearly 40 per cent. of the total energy of a tumor may come from the glycolytic process alone. And, it has been shown by Okamoto[88] that both the Rous sarcoma and the Jensen rat sarcoma can be kept alive under anaerobic condition, and Wind[89] has succeeded in cultivating Rous sarcoma in the virtual absence of oxygen. The cancer cell, it would seem, does not need much oxygen.

That the same marked glycolysis actually occurs in vivo has been shown by Tadenuma[90] and by Cori[91] who observed that blood passing through a sarcomatous wing of a fowl lost more sugar than that passing through a normal wing. This observation has been amplified by Warburg[92].

As regards the classification of cells, Warburg points out that normal adult tissues show a high rate of oxygen consumption and but little glycolysis, while embryonic tissue shows both high respiration and high glycolysis under anaerobic conditions, but only slight glycolysis under aerobic conditions, and neoplastic tissue has a rather low respiration rate and a high glycolysis under both aerobic and anaerobic conditions (Table 1).

TABLE 1

Tissue	Aerobic Glycolysis	Anaerobic Glycolysis
Normal	Slight	Slight
Embryo	Slight	Great
Tumor	Great	Great

In his general conclusions he has been supported by Rona and Deutch[93], Murphy[94] and Waterman[95]. But, Murphy would classify the chorion as a malignant tumor and the spleen as embryonic, and the author has found (unpublished experiments) that certain malignant human sarcomata have a virtually normal metabolism. Rosenthal has come to the same conclusions (213). There are even in Warburg's own figures two notable exceptions to the general classification, namely, the gray matter of the brain and the retina, both of which behave as malignant neoplasms.

In an effort to eliminate these discrepancies, Warburg[96] has resorted to a new value on which to classify tissues. He points out that when the Pasteur reaction functions at its maximum, exactly two molecules of lactic acid are suppressed when one molecule of oxygen is consumed, and, on this basis he suggests as a new value "U", which is the aerobic glycolytic rate when the Pasteur reaction is unrestricted by artificial experimental conditions. Of course, this being a somewhat arbitrary and artificial figure, the value may be a negative quantity when the respiratory rate is so great as completely to overbalance the glycolysis.

In a recent paper[96] he gives the accompanying table (Table 2), where Q_{O_2} is the respiratory rate, $Q^{N_2}_m$ the anaerobic glycolysis, and U the "excess glycolysis".

TABLE 2

Tissue	Q_{O_2}	$Q^{N_2}_m$	U
Rat kidney	—21	+3	—39
Rat liver	—12	+3	—21
Rat spleen	—12	+4	—20
Rabbit pancreas	—5	+3	—7
Dog pancreas	—3	+4	—2
Rat embryo (3 mgm.)	—12	+13	—11
Hen embryo (1.7 mgm.)	—10	+20	±0
Rat placenta	—7.3	+14.9	+0.3
Nasal polyp	—5	+14	+4
Bladder carcinoma	—10	+36	+16
Flexner-Jobling carcinoma	—7	+31	+17
Rous sarcoma	—5	+30	+20
Retina	—31	+88	+26
Human skin carcinoma	—3.1	+13.8	+7.7
Human mammary carcinoma	—2.6	+11.1	+5.9

He further notes in the same article that red blood cells yield positive values for "U" and so they, together with the retina, remain, for the present at least, as exceptions to the general rule.

These probable facts have been combated by Bauer and Nyiri who claim that human carcinoma does not produce any more lactic acid than normal tissue. But Warburg[96] has pointed out that the amount of glycolysis depends, of course, upon the actual number of cancer cells and is, furthermore, very sensitive to changes in the medium. One must, therefore, be cautious in drawing conclusions from human material, in which connective tissue stroma often is far out of proportion to the actual malignant tissue. Rona and Deutsch[93] confirm Warburg as regards human material, though their results, it must be confessed, are much lower than his. Blanchetiere[98] also confirms Warburg. It is further of interest that Cori and others have found, as has been mentioned above[90, 91], that the lactic acid content of the blood is raised by passing through a malignant process, and it would seem, therefore, that the increased glycolytic power of cancer tissue is also found in vivo.

There is no question but that Warburg's work is upon a firm foundation and it certainly offers a convenient starting point for the study of fundamental carcinomatous processes.

As regards the origin of cancer, Warburg is conservative. He offers as a suggestion that some cells of normal tissue may have all the metabolic activities of neoplastic cells, and that these, under conditions of chronic anoxemia in which the normal cells may be killed, possess sufficient anaerobic glycolytic activity to allow them to develop into a malignant growth.

The field of the chemical metabolism of tumors lies open to those investigators who wish to study cancer, and great opportunities are afforded for the advance of the understanding of the fundamental process of growth.

THE CHEMOTHERAPEUSIS OF CANCER

Many chemical substances, chiefly the heavy metals and the dyes, have been tried in the treatment of carcinoma[80, 99, 100]. The Egyptians and Arabians are said[80] to have used arsenic in the treatment of malignant disease, and this substance was employed intermittently throughout the middle ages. As late as 1913, Emil Fisher[101] advocated the use of an organic arsenic compound. More recently Sugiura and Benedict[102] showed that in animals arsenic had a slightly retarding effect on the growth of cancers. Iodine, silicon, iron, potassium, and calcium have all been advocated[80], but with none has any degree of success been attained. Sugiura and Benedict[102] have made an exhaustive study of the effects of various salts on the Flexner-Jobling rat carcinoma, and they conclude that copper, arsenic, potassium, and calcium have a slight retarding effect on the tumors, while magnesium accelerates the growth somewhat and telurium and selenium have no effect on the tumor, though a marked deleterious effect on the animal. Soiland[103] concludes that neither colloidal gold, colloidal copper, nor colloidal lead is of value. Lewin[104] agrees, so far as gold is concerned. Gillette[105] finds selenium too toxic. Wassermann and Keyser[106] advocated for a time a selenium-eosin compound, and Kausch[107] used silver, but found it very toxic. Copper, though advocated by several, was finally discarded, after an exhaustive study, by Weil[108]. Numerous dyes have been tried[101, 80], and Roosen[109] has claimed beneficial results with isamin blue, and in this respect Yabusoe's[130] work on the influence of dyes in vitro may be recalled. But Simpson[110] failed to produce beneficial results with any of 33 coal tar dyes. For a more complete review of all the substances that have been tried in combating carcinoma, the reader is referred to the monographs of Kaminer[80] and Waterman[100].

As long ago as Galen, lead was used in the treatment of carcinoma. It was again advocated by Goulard in the eighteenth century[111]. It remained for Blair Bell of Liverpool to bring

out a lead treatment which has aroused much interest. Bell[112, 113, 114, 115, 116, 117], starting with the theory that the chorion is essentially a malignant tissue, attempted to isolate from the foetus the substance which he thought brought about the cessation of growth of the chorion and consequently normally prevented it from becoming a malignant tumor. This search was unavailing and he therefore turned his attention to the known abortifacients. He remembered that lead frequently brought about abortion in animals and women, and he determined to try the effect of lead upon carcinomatous tissue. His theory for so doing depends essentially upon his conception of the chorionic epithelium as being fundamentally a malignant tissue, and in favor of this view he brings forward considerable evidence. He points out that lead is toxic to many normal tissues (brain, gonads, blood) and especially so to actively growing tissues. He finds, for instance, that lead salts in small concentration will kill hyacinth bulbs, and that concentrations of 1 to 100,000 will prevent the germination of frogs' eggs, whereas the adult frog can stand concentrations of 1 to 1000[112]. Assuming, as he does, that "the primary metabolic factors associated with neoplasia are the same in both types (innocent and malignant)—indeed in all types of growth, he builds up a logical basis for the "treatment of every malignant growth with preparations" of lead. It may be objected that some of his facts need substantiation and that a substance toxic for normal adult tissue in relatively small amounts is not ideal as a chemotherapeutic agent against neoplastic disease on account of the almost certain narrow margin of safety. He claims, however, that lead concentrates in the cancerous tissue to a greater extent than in other tissues, except the testis. In this respect, Waterman[100, 118] does not agree, as he finds more lead in the normal tissues than in the cancer. Martland[119] found no histological evidence of the presence of lead in his human cases, nor did he find, on chemical analysis, that the lead was in greater amounts in the tumor. The theory, however, is less important than the clinical facts.

Bell originally used inorganic and organic lead compounds, but finally came to employ colloid lead. This was prepared[112, 114] by Bredig's sparking method in an aqueous solution. The final solution, as used, contained approximately 0.5 per cent. lead and was not stable, except for short periods of time. This colloidal solution was injected intravenously in doses of about 50 to 100 mgm. over a period of weeks. Bell advocates the removal, surgically, of as much of the tumor as possible, and cautions against the use of lead in tumors of the lung or brain, in obstructive jaundice, and in cases where the blood is anemic or when chronic nephritis, even of a slight grade, is present. His last published figures are as follows[114]:—

Admitted but died before treatment could be started	20
Died before treatment could be completed	50
Died of intercurrent affections	3
Died after treatment	106
Too recent for results to be estimated	14
Died as a result of extensive destruction of the tumor by lead	4
Complete treatment refused but patients leading normal lives	9
Disease completely arrested	10
Believed cured	31

As regards the direct effect of lead on the tumor, there is some difference of opinion. Glynn[120] found few striking histological changes. Fry[121], likewise, found little evidence suggesting the destruction of the tumor by lead, though he did find that the kidneys showed extensive tubular degeneration. Wood[99, 122], however, noted in animals marked necrosis of the neoplastic tissue and thrombosis of the vessels supplying the tumor; and others have noted apparent massive necrosis of human tumors[123].

No doubt some cases have been benefited; how many, it is impossible at this time to say. Other authors fail, however, to get such promising results as Blair Bell. Todd[215] found clinical improvement in 7 of a large series of patients. Knox[216], using lead and x-ray, had promising results in 8 cases out of 40. Ullman[123, 124] found that when using colloid metallic lead his patients often suffered from lumbar pain, hematuria and acute nephritis, and that the hemoglobin fall was marked and rapid. For these and other reasons, he changed to a colloidal lead phosphate—a very logical change in view of the fate of lead when injected into the body—and found that this compound was much less toxic to the organism as a whole. Ullman now advocates the lead phosphate and reports favorably on its use. The continued use of lead and radiation has been suggested by several. Martland[131] preparing his colloidal metal in a different manner, reports that in 15 cases there was only a temporary improvement, and he feels that no effect is produced on the tumor unless thrombosis is brought about. Wood[99], on the contrary, says, "For the first time a substance has been found that will arrest the growth of carcinoma for a period of from one to five years, and this in patients both inoperable and beyond the power of irradiation to effect a cure." Stone and Carver[125] review the subject very completely and report their own results from the Memorial Hospital, New York. Their lead colloid was prepared most carefully by a modified Bredig's method and was stable over a considerable period of time. They found no serious immediate symptoms or serious after effects except anemia, and from this the patient rapidly recovered when lead was temporarily omitted. They saw appreciable regressions in 4 out of 7 mammary cancers and in 2 a "temporary cure". There seemed, also, to be some benefit in 3 cases of osteogenetic sarcoma and one case of Ewing's tumor. It is interesting in view of Bell's original theory to note that the treatment failed completely in the case of a chorioepithelioma of the

vagina. They conclude that lead does not offer a general cure for malignant neoplasms, but that in mammary cancer and osteogenetic sarcoma it may—either alone or with x-ray—be of value. Wood[126], working with rat tumors, finds evidence that lead increases the sensitivity of the tumors to x-ray and advocates a combined treatment. Ullman joins in this recommendation.

It is probably still too early to say whether or not lead will take a permanent place in the therapy of cancer. Bell's results are certainly encouraging. Other authors have not been so successful. More work will have to be done in a very carefully controlled manner and several years will elapse before the true value of the substance is known. It can be said, however, that at the present writing it is not a treatment to be attempted outside of a fully equipped and well organized research hospital under the charge of both expert clinicians and expert chemists.

REFERENCES

1 Paget: Cited by Ewing. J. Neoplastic Diseases, N. Y., 1928.
2 Lebert: Cited by Ewing. J. Neoplastic Diseases, N. Y., 1928.
3 Sibley: Cited by Ewing. J. Neoplastic Diseases, N. Y., 1928.
4 Crips: Cited by Ewing. J. Neoplastic Diseases, N. Y., 1928.
5 Hillier and Tritsch: Arch. Middlesex Hosp., 2, 1904, 104.
6 Bashford: Proc. Royal Soc., 2, 1909, 63.
7 Weinberg: Zeit. f. Krebs, 2, 1904, 195.
8 Little, C. C.: Eugenics, Genetics, and the Family, 1, 1923, 188.
9 Bashford, and Murray, J. A.: Imp. Can. Res. Reports, 1911, 114.
10 Loeb, L.: Med. Bull. Univ. Penn., 1907.
11 Tyzzer, E. E.: Jour. Med. Res., 11, 1907, 199.
12 Tyzzer, E. E.: Jour. Med. Res., 16, 1909, 479.
13 Tyzzer, E. E.: Jour. Med. Res., 19, 1909, 519.
14 Slye, M.: Jour. Med. Res., 25, 1914, 218.
15 Slye, M.: Jour. Med. Res., 27, 1915, 159.
16 Slye, M.: Jour. Cancer Res., 1, 1916, 479.
17 Slye, M.: Jour. Cancer Res., 2, 1917, 213.
18 Slye, M.: Jour. Cancer Res., 5, 1920, 25.
19 Slye, M.: Jour. Cancer Res., 7, 1922, 107.
20 Slye, M.: Jour. Cancer Res., 7, 1922, 104.
21 Slye, M.: Jour. Cancer Res., 8, 1924, 240.
22 Slye, M.: Radiology, 4, 1925, 7.
23 Slye, M.: Jour. Amer. Med. Assoc., 86, 1926, 1599.
24 Slye, M., Holmes, H. F., and Wells, H. G.: Jour. Cancer Res., 10, 1926, 175.
25 Slye, M.: Jour. Cancer Res., 10, 1926, 15.
26 Slye, M.: Jour. Cancer Res., 11, 1927, 135.
27 Slye, M.: Jour. Cancer Res., 11, 1927, 54.
28 Cockayne, E. A.: Cancer Review, 2, 1927, 337.
29 Little, C. C.: Harvey Lectures, 1921-1922, 65.
30 Little, C. C.: Commonwealth Rev., 1926-7-8-9-1.
31 Murray, W. S.: Science, 1927, lxvi, 600.
32 Fibiger, K.: Zeit. f. Krebs., 13, 1913, 217; 14, 1914, 295.
33 Bullock, F. D., and Curtis, W. R.: Trans. N. E. Path. Soc., 20, 1920, 149.
34 Blumenthal, F.: Deutsch. Med. Wochens, 52, 1926, 389.
35 Blumenthal, F.: Deutsch. Med. Wochens, 52, 1926, 1284.
36 Nuzum, J. W.: Surgery, Gyn. and Obs., 33, 1921, 167.
37 Nuzum, J. W.: Surgery, Gyn. and Obs., 40, 1925, 343.
38 Gye, W. E.: Lancet, 2, 1925, 109.
39 Gye, W. E.: Lancet, 2, 1926, 989.
40 Gye, W. E., and Andrews: Brit. Jour. Exp. Path., 7, 1926, 81.
41 Gye, W. E.: Brit. Med. Jour., 2, 1926
42 Rous, P.: Jour. Exp. Med., 13, 1911, 397.
43 Rous, P., and Murphy, J. B.: Jour. Exp. Med., 19, 1914, 52.
44 Rous, P., and Murphy, J. B.: Jour. Exp. Med., 19, 1914, 52.
45 Murphy, J. B.: Jour. Amer. Med. Assoc., 86, 1926, 1270.
46 Murphy, J. B.: Amer. Naturalist, 60, 1926, 227.
47 Flu, P. C.: Zentr. f. bact. parasit. u. Infect., 99, 1926, 332.
48 Flu, P. C.: Afd. trop. hyg. inst. v. trop. geneesk., 70, 1926, 336.
49 Mackensie, R. D., and Illingsworth, C. F. W.: Lancet, 2, 1926, 745.
50 Harkins, M. J., Shamberg, J. F., Kolmer, J. A., and Kast, C. M.: Jour. Cancer Res., 10, 1926, 66.
51 Muller, J. H.: Jour. Exp. Med., 45, 1927, 243.
52 Baker, S. L., and McIntosh, J.: Brit. Jour. Exper. Path., 10, 1928, 257.
53 Cutler, M.: Jour. Cancer Res., 10, 1927, 450.
54 Ewing, J.: Neoplastic Diseases, 1928.
55 Burrows, M. T.: South. Med. Jour., 17, 1924, 233.
56 Burrows, M. T.: Radiology, 4, 1925, 407.
57 Burrows, M. T., and Johnson, C. S.: Arch. Int. Med., 36, 1925, 294.
58 Burrows, M. T.: Jour. Cancer Res., 10, 1926, 239.
59 Burrows, M. T.: Arch. Int. Med., 37, 1926, 453.
60 Burrows, M. T.: Jour. Med. Res., 44, 1924, 643.
61 Jorstad, J. H.: Jour. Cancer Res., 9, 1925, 232.
62 Burrows, M. T.: 17th Int. Congress Med., Gen. Path. Anat., London, 1913, 217.
63 Burrows, M. T.: Am. Jour. Physiol., 77, 1926, 38.
64 Carrel, A., and Burrows, M. T.: Jour. Am. Med. Assoc., 56, 1911, 32.
65 Robertson, T. B.: Biochem. Jour., 15, 1921, 596.
66 Sugiuria, and Benedict, S. R.: Jour. Cancer Res., 3, 1920, 373.
67 Burrows, M. T., and Jorstad, L. H.: Am. Jour. Physiol., 77, 1926, 24.
68 Jackson, H. Jr., and Krantz, C. I.: J. Clin. Invest., 1929, 6, 609.
69 Wyard, S.: Lancet, 1, 1922, 840.
70 Lapidari, M.: Riforma Med., 42, 1926, 891.
71 Ludwig, F.: Zeit. f. Krebs., 23, 1926, 2.
72 Kramer, N.: Zeit. f. Krebs., 1924, 21.
73 Fujimaki, Y., Kimura, T., Wada, Y., and Shimada, S.: Gann., 21, 1927, 8.
74 Wolbach, S. B., and Howe, P. R.: Arch. Path. and Lab. Med., 4, 1927, 492.
75 Wolbach, S. B., and Howe, P. R.: Jour. Exp. Med., 42, 1925, 753.
76 Goldblatt, H., and Benischek, M.: Jour. Exp. Med., 46, 1927, 699.
77 Muller, J.: Bei. d. Kgl. pruss. Akad. d. Wissenschaften, 1836.
78 Freund, E., and Kaminer, G.: Biochemische Grundlagen der Disposition f. Karzinom, 1925.
79 Harpuder, K.: Dermat. Wochenschr., 83, 1926, 1579.
80 Kaminer, S.: Die Biochemie des Karzinoms, 1926, 27.
81 Warburg, O., et al.: Ueber den Stoff wechsel der Tumoren, Berlin, 1926.
82 Warburg, O.: Klin. Wochensch., 4, 1925, 534.
83 Minami, S.: Biochem. Zeitschr., 142, 1923, 334.
84 Warburg, O., Posener, K., and Negelein, E.: Zeitschr., 152, 1924, 309.
85 Fahig, C.: Zeitschr. f. Krebs., 25, 1927, 146.
86 Warburg, O.: Jour. Cancer Res., 9, 1925, 148.
87 Meyeroff, O.: Jour. Gen. Physiol., 8, 1927, 531.
88 Okamoto, Y.: Biochem. Zeitschr., 160, 1925, 52.
89 Wind, F.: Klin. Wochenschr., 5, 1926.
90 Tadenuma, K., Hotta, S., and Homma, J.: Biochem. Zeit., 137, 1923, 536.
91 Cori, C. F., and Cori, G. T.: Jour. Biol. Chem., 64, 1925, and 65, 1925, 397.
92 Warburg, O., Wind, F., and Negelein, E.: Klin. Wochenschr., 5, 1926, 829.
93 Rona, P., and Deutsch, W.: Klin. Wochenschr., 5, 1926, 1216.
94 Murphy, J. B., and Hawkins, J. A.: Jour. Gen. Physiol., 8, 1925, 115.
95 Waterman, N.: Ber. Ges. Physiol. Exp. Pharm., 29, 1925, 384.
96 Warburg, O.: Biochem. Zeitschr., 184, 1927, 484.
97 Warburg, O.: Klin. Woch., 5, 1926, 2119.
98 Blanchetiere, A.: Bull. de l'Assoc. franc. pour l'etude du cancer, 16, 1927, 3.
99 Wood, F. C.: Jour. Am. Med. Assoc., 87, 1926, 717.
100 Waterman, N: Die Heutige Stand Chemotherapeutischen Carcinomforschung, 1926.
101 Fisher, E.: Therapie der Gaegenwart, 1913.
102 Sugiura, K., and Benedict, S. R.: Jour. Cancer. Res., 7, 1922, 39.
103 Soiland, A., Costolow, W. E., and Meland, O. N.: Radiology, 8, 1927, 469.
104 Lewin, C.: Berlin. Klin. Wochenschr., 8, 1913, 541.
105 Gillette, A. S., and Wakeley, C. P. G.: Brit. Jour. Surg., 9, 1922, 532.
106 Wassermann and Keyser: Deut. Med. Wochenschr., 37, 1911, 2389.
107 Kausch: Arch. f. Klin. Chir., 102, 1913, 159.
108 Weil, R.: Jour. Am. Med. Assoc., 61, 1913, 1034.
109 Rosen, R.: Zeitschr. f. Krebs., 24, 1926, 35.
110 Simpson, B. T., and Marsh, M. C.: Jour. Cancer Res., 10, 1926, 50.
111 Weller, C. V.: Ann. of Clin. Med., 5, 1927, 753.
112 Bell, W. B.: Lancet, 1, 1924, 267.
113 Bell, W. B.: Lancet, 2, 1925, 1003.
114 Bell, W. B.: Lancet, 1, 1927, 537.
115 Bell, W. B.: Brit. Med. Jour., 1, 1926, 687.
116 Bell, W. B.: Brit. Med. Jour., 2, 1926, 919.
117 Bell, W. B.: Brit. Med. Jour., 2, 1926, 934.
118 Waterman, N.: Compt. Rend. Soc. de Biol., 94, 1926, 724.
119 Martland, H. S., von Sockocky, S. A., and Hoffman, H.: Jour. Am. Med. Assoc., 88, 1927, 911.
120 Glynn, E. E.: Brit. Med. Jour., 2, 1926, 928.
121 Fry, H. J. B.: Brit. Imp. Cancer Campaign Ann. Report, 1927, 32.
122 Wood, F. C.: Brit. Med. Jour., 2, 1926, 928.
123 Ullman, H. J.: Jour. Am. Med. Assoc., 89, 1927, 1218.
124 Ullman, H. J.: Radiol., 8, 1927, 461.
125 Stone, W. S., and Craver, L. F.: Ann. of Surgery, 86, 1927, 347.
126 Wood, F. C.: Jour. Am. Med. Assoc., 89, 1927, 1217.
127 Rosenthal, O., and Lasuitz, H.: Biochem. Zeit., 1928, 192, 340.
128 Ullman, H. J.: Jour. Am. Med. Assoc., 1929, 92, 18.
129 Wells, H. G.: Jour. Am. Med. Assoc., 88, 1927, 339, 476.
130 Yabusoe, M.: Biochem. Zeit., 168, 1926, 227.
131 Martland, H. S.: Jour. Am. Med. Assoc., 88, 1927, 911

THE SURGICAL TREATMENT OF EMBOLISM OF THE EXTREMITIES*

BY ARTHUR W. ALLEN, M.D., F.A.C.S.†

THE first report of the successful removal of an embolus from a large artery was made in 1911 by Mosny and Dumont; they related in detail the history of a thirty-eight year old cardiac patient who, while under treatment in the hospital for his heart condition, suddenly developed severe cramp-like pains in the calf of his left leg. The affected extremity rapidly became cold to a hand's breadth above the patella and insensitive from the toes to the knee joint. The muscles of the foot and leg were powerless. No pulsation could be felt in the tibial or popliteal vessels. Pulsation could be detected in the upper part of the femoral triangle. Six hours after the onset of the symptoms of embolism, M. Georges Labey opened the artery, in Scarpa's triangle, under local anesthesia and removed a bifid clot from the bifurcation of the common femoral. Two hours later the leg was warm. The next day popliteal pulsation was palpable and thirty-six hours after the operation, pulsation could be felt in the posterior tibial artery. An uneventful convalescence followed. This typical story has been repeated many times since Labey's success and embolectomy has become a standardized surgical procedure.

Known unsuccessful attempts to relieve these patients surgically had been made as early as 1895 by S. Sabanejew and by Moynihan in 1897, Stewart in 1907, Debenauer in 1907, Proust in 1908, Schiassi, Murphy, Carrell and Leriche in 1909. To Carrell must be given much credit in making these operations possible, as he first developed a successful technique of arterial suture. To Einor Key, however belongs the credit of popularizing embolectomy by his many articles on the subject and his unparalleled success in this field of surgery. In 1928 he reported ninety-five cases operated upon in Sweden, seventeen of these having been done by himself on fifteen patients.

In view of the ever increasing literature on the subject, it seems safe to estimate that at least a like number have been performed elsewhere in the world. Approximately 30% of all reported cases have been successful and doubtless many failures have never appeared in the literature.

INCIDENCE, SOURCE AND LOCATION OF EMBOLI

Bull studied the problem of emboli in over six thousand autopsies, and found in this number fifteen incidences of peripheral emboli, located as follows:

Aorta	2
Common Iliac	6
Femoral	5
Popliteal	1
Subclavian and Axillary	1

Six had definite gangrene, seven no gangrene, and two were doubtful. In all but one case emboli were found in other organs.

He also found:

181 Thrombi in 6140 hearts
67 Thrombi in the Right heart
63 Thrombi in the Left heart
51 Thrombi in both

Dschanelidze, in analyzing 109 cases of embolectomy in 1927, found the following distribution:

Femoral Artery	50
Iliac Artery	16
Aorta	14
Brachial	13
Popliteal	9
Axillary	4
Subclavian	1
Radial	1
Ulna	1

Approximately one-half the emboli occurred in patients with heart disease. Eleven cases followed infectious diseases. In thirty-four cases the cause was not determined.

Danzis reports on thirty-seven collected cases of embolectomy as follows:

Upper Extremity		11
Axillary Artery	5	
Subclavian Artery	1	
Brachial Artery	5	
Lower Extremity		26
Bifurcation of Aorta	2	
Femoral Artery	18	
Iliac Artery	4	
Popliteal Artery	2	

The reason for this high proportion affecting the upper extremity is probably due to the relatively higher degree of success of the operation in the upper extremity and therefore the more frequent reports on these cases.

He also classifies thirty-seven cases as to etiology as follows:

Post Operative	6
Parturition	3
Cardio-Vascular Disease	22

Pemberton reports that at least 21 cases of peripheral emboli occurred in 200,000 admissions to the Mayo Clinic.

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†For record and address of author see "This Week's Issue," page 339.

TIME INTERVAL BETWEEN ONSET AND SUCCESSFUL OPERATION

(Quoted by Loretti)

Key analyzed 36 cases as follows:

No. of Cases	Hours Elapsed	Recovery	Death
10	5	7	3
8	10	4	4
8	15	2	6
4	20	1	3
6	24	2	4

(Quoted by Lundberg)

He analyzed 45 cases as regards successful restoration of the circulation, as follows:

No. of Cases	Hours Elapsed	Success
12	2 or less	9
5	11 to 15	2
4	16 to 24	1

One case only has been reported with a successful outcome with a duration of over twenty-four hours, and that was a brachial embolus removed by Key forty-eight hours after onset of symptoms.

DIAGNOSIS AND LOCALIZATION

The diagnosis is often obvious. A patient already ill, usually a cardiac, suddenly is stricken with excruciating, knife-like pain in an extremity. The pain persists and requires large doses of opium to control. There is an elevation of pulse and respiration, a definite pallor and a lowering of the pulse pressure; sweating and other evidences of shock are apparent. Locally the limb affected is cold and pale and there is inability to move the toes or fingers. Pulsation is absent in the peripheral arteries. Later the limb becomes mottled in color and colder, and the digits have a fixed, drawn appearance. There is contraction of the tissues and not swelling. Differentiation from a thrombosis, which takes place more slowly, is often difficult, and frequently there is built up a rapid extensive thrombosis on a relatively small and harmless embolus. It is in this class of case that we find most of our failures. Phlebitis can be differentiated by the presence of swelling, bluish coloration, heat, and pulsating vessels. Muscle spasm from temporary anaemia is too transient to be confusing.

The greatest aid in localization is the knowledge of the fact that emboli nearly always lodge at a bifurcation, coming to rest at a point in the artery too small to allow further progress toward the periphery. If seen early, before secondary thrombus formation is too extensive, the site of the embolus can usually be determined. If it is in the popliteal artery, the femoral can be felt pulsating in Hunter's canal, and the decrease in temperature stops about the ankle. Ankle motion is usually possible. If it is at the bifurcation of the common femoral, the temperature of the skin is lowered to a short distance above the knee and the lowest point of pulsation is just below Poupart's ligament. Voluntary ankle and toe motion is abolished. If the embolus has come to rest at the bifurcation of the common iliac, the whole thigh is cold, no pulsation is felt on that side, and voluntary knee motion may be abolished. The embolus may be definitely palpable, especially at the bifurcations of the brachial and the femoral arteries.

RESULTS

The most optimistic report was made by Dshanelidze, in his analysis of one hundred and nine cases, in which he states that permeability of the blood vessel was established in 39.4% of the series. He does not state, however, whether some of these cases go to make up part of his group of the thirty-eight per cent. who died.

The greatest number of successes were operations for embolism on the brachial artery (sixty-eight per cent.). Embolectomy of the femoral, popliteal and iliac arteries resulted in recovery in thirty-three per cent., while removal of emboli from the bifurcation of the aorta was least successful.

Key reports at least one successful embolectomy from the aorta by the retrograde approach through the femorals.

The average percentage of successful operations is given by most writers as thirty. Allowing for the difference of opinion as to successful restoration of the circulation and the patient's ability to leave the hospital with a normal extremity, it seems safe to estimate that twenty-five per cent. of embolectomies should be entirely successful.

TECHNIQUE OF OPERATION

The operation should always be done under local, regional, or spinal anesthesia, a sufficient amount of medication being given to produce comfort. A liberal incision should be made to expose the artery a few centimeters above and below the embolus. Care must be taken to handle the artery gently, as the embolus may be dislodged and carried further towards the periphery. As soon as the artery is thoroughly freed from all adjacent structures, six inch lengths of rubber tubing of the same calibre as the artery, as advocated by Michaelson, are placed beneath the two branches distal to the embolus and above on the main trunk. A hemostat, holding the two ends of the tubing together, gives good control of the situation. These are left slack except when needed. Sufficient tension should be kept on the distal ones by an assistant to prevent the embolus from traveling toward the periphery during the necessary manipulations. Harrington tape, or even Crile clamps, may be used to control the vessels. Every effort, however, should be exerted to avoid injuring the intima. The wound should then be protected by

gauze saturated with two per cent. sodium citrate solution, and instruments and gloves frequently washed in the same liquid. The artery is then opened longitudinally, the incision being from 1 to 2 cm. in length and placed just above or at the upper end of the embolus, which is then milked out through the opening by gentle pressure on the artery from below. As soon as all the obstruction is removed from the two main radicals below the incision, there is free back bleeding into the wound. The distal arteries are now controlled by the tourniquets in the hands of an assistant and the upper portion of the embolus or secondary thrombus is allowed to be extruded by the force of the blood stream. It may be necessary first to loosen the obstruction above by means of a probe dipped in sterile oil, great care being taken not to injure the edges of the wound or the intima. As soon as the obstruction has been removed, the incision in the artery is closed with very fine silk on a Carrel arterial needle, both of which have been immersed in sterile oil. The artery should be closed so as to bring the intima along the edges in apposition; a running mattress is sufficient; a shoemaker's stitch can be used, or a carefully applied simple over-and-over, provided care is taken that the edges do not roll in. Care should be used to have the sutures taut so that no silk is exposed on the inside of the artery, as this lends itself to thrombus formation. If the site of the embolus is the bifurcation of the common iliac artery or the abdominal aorta, a retrograde removal through incisions in one or both femoral arteries is more successful than a direct abdominal approach. The probing should be done with smooth rounded instruments and never with sharp curettes. A special instrument for this purpose has been described by Pemberton, and Odelberg calls attention to the use of a flexible spiral varix instrument devised by Babcock and Rissler, particularly in the removal of distal secondary thrombi. Uterine probes and olive tipped bougies or catheters are helpful. The incision may be extended on occasions and the clot broken up by direct pressure on the artery.

CASE REPORTS

CASE 1

M. S.—263731 June 21, 1924

J. S., female, aged 46, a diabetic, was awakened, one morning, with great pain, together with coldness and numbness of her left hand and forearm. She came to the hospital three days later with the hand shriveled, cold and insensible; she could not move the fingers. No pulsation was felt below the brachial artery. A mass could be felt at the lower end of the brachial artery.

After novocain infiltration, the artery was exposed and opened above the mass. A bifid thrombus was milked from the radial and ulna arteries, and the artery closed. Gangrene progressed. Amputation, ten days later, five centimeters above the condyles, was followed by recovery.

CASE 2

E. S.—268776 April 16, 1925

J. K., a female, aged 50, a hypertensive cardiac with fibrillation, entered the hospital April 6, 1925. Thrombosis of the veins of the chest wall occurred ten days after admission. She complained of severe pain in the right leg, the same evening. The next morning the leg was cold to the mid thigh, blue and mottled. There was no pulsation below Scarpa's triangle.

Under novocain infiltration the common femoral artery was exposed and opened above the bifurcation. A thrombus ten and one-half inches long was milked out of the superficial femoral artery, and the artery sutured. Gangrene set in, demarcated at the junction of the upper and middle thirds of the leg. Gritti-Stokes amputation was performed nine days later from which a good recovery was made.

CASE 3

W. S.—269546 June 29, 1926

J. R., female, aged 64, a diabetic with auricular fibrillation and arteriosclerosis, awakened, one morning, with severe pains in both legs. She crawled to the bathroom. Twelve hours later she was brought to the hospital. Both legs were cold and mottled half way to the knees. Pulsation was felt in both superficial femorals, but no pulsation in either popliteal artery.

Under anesthesia the right popliteal artery was exposed, and opened at the upper level of an embolus, which was removed with forceps. The patient suddenly died fifty minutes after the anesthetic had been started. She had received only 2½ ounces of ether.

CASE 4

E. S.—291203 May 14, 1928

E. S. Mc., a female aged 78, recovering from pneumonia, and a severe hypertensive cardiac of several years standing, with recent auricular fibrillation, entered the hospital May 14, 1928. She had had severe cramp-like pain in the right leg on the evening prior to admission, which had subsided under morphia. She awakened at 6 A. M. on the day of admission with recurrence of pain in the right leg, which was found to be cold and insensible. Pulsation was only felt just below Poupart's ligament. She was sent to the hospital in an ambulance.

Under novocain infiltration the femoral artery was exposed and opened just above the bifurcation, six hours after the second attack of pain. A large embolus was extruded by force of the blood stream. The artery was closed. The leg became warm in a few hours. The next day the patient was very ill and irrational; both legs were cold and mottled to the knees. She died two days after admission.

CASE 5

E. S.—283393 July 5, 1928

D. S., male, aged 60, entered this hospital July 5, 1928 with cerebrospinal lues and arteriosclerosis and senile gangrene of right foot. Non-specific foreign protein of 75 million typhoid vaccine was given. One hour later he complained of severe pain in the left leg. Eighteen hours following the onset the left leg was cold and mottled to the tibial tubercle; pulsation was felt in the superficial femoral artery.

Under novocain infiltration, the popliteal vein was ligated and divided, the popliteal artery was opened and a large bifid clot removed. The artery was sutured. The leg became warm and all of the foot except the tips of his toes cleared up. Three days later he developed a return of pain in his left leg, with no pulsation below Scarpa's triangle. Operation was performed by Dr. R. H. Smithwick, who removed a clot from the superficial femoral artery. The clot reformed as soon as the vessel was sutured. A left

mid-thigh amputation was done twelve days later; and a right mid-thigh amputation by Dr. D. F. Jones two and one-half months later. Death occurred at his home December 29, 1928.

CASE 6

E. S.—264351 July 17, 1928

A. B., female, aged 48, had had a subtotal thyroidectomy in 1924 for exophthalmic goitre by Dr. C. A. Porter. Her heart was typical of severe Graves' disease. July 17, 1928 she entered the hospital with fever of unknown origin, thought to be typhoid. She had sudden cramp-like pains in right leg. No pulsation was felt below Scarpa's triangle.

Three hours after onset, under novocain infiltration, the common femoral was exposed and the artery opened just above the embolus. A large bifid clot was removed by pressure from below. There was immediate bleeding from both branches. The popliteal pulse was felt as soon as the wound was closed. Two days later the dorsalis pedis and the posterior tibial pulses could be felt. The day folowing embolectomy, the patient complained of severe pain in the left upper quadrant, from which she slowly recovered; this pain was probably from an infarct in the spleen. The embolus from the artery was cultured and staphylococcus albus was recovered. She was discharged relieved August 24, 1928, one month following embolectomy. The patient was in good health in May, 1929. She has noticed slight swelling on the inner surface of thigh below the operative wound, at the end of the day, which may be due to some interference with the lymphatics in this region.

CASE 7

E.S.—297026 February 15, 1929

G. M., a female, aged 30, with chronic rheumatic heart disease had an abortion by abdominal hysterotomy at the Boston Lying-In Hospital on February 6, 1929, after one month of ineffective bed treatment for her heart condition. February 15 she had sudden severe pain in right leg. Eight hours later the leg was cold and insensitive to the knee. She could move her toes slightly. No pulsation could be felt throughout the extremity. A diagnosis of iliac embolism was made.

Under novocain infiltration the femoral artery was exposed in Scarpa's triangle; the artery was small and did not pulsate, but when it was opened there was some bleeding. The artery was probed proximally but no clot was extruded. The amount of bleeding, however, was increased. The patient was in a very critical condition on the table and had Cheyne-Stokes respiration. The artery was closed and she was transferred to the Massachusetts General Hospital. On February 18 a mid thigh amputation was done. Sudden death occurred February 25, 1929, probably from pulmonary embolism.

SUMMARY OF PERSONAL CASES

Six embolectomies in seven attempts are reported: one brachial, one popliteal, and four femoral.

Three out of seven patients died in the hospital.

Three patients had temporary restoration of circulation.

One patient has permanent restoration of circulation (bifurcation of the femoral).

Three of the four surviving cases required amputation.

CONCLUSIONS

Embolectomy is a definitely standardized surgical procedure. The diagnosis should frequently be made early and without difficulty. The earlier the diagnosis and operation, the more favorable the result. Certainly cases occurring in and nearby large hospitals should be operated upon. Delay beyond a favorable time for operation can almost always be avoided, if the physician in charge of the case is alert to the condition.

BIBLIOGRAPHY

Bani, Ugo: Embolectomy, the ideal treatment of embolic disturbances in the limbs. Policlinics (sez. chir.), 35:117-135, March, 1928.

Buerger, L.: Operative treatment of embolism of large arteries; report of 2 cases. Surg., Gynec. and Obstet., 36:463, 1923.

Bull, P.: What can more than 6000 post mortem examinations teach us about emboli and embolic gangrene of the extremities. Act. Chir. Scandin., 54:315, 1922.

Connors: Embolism of the brachial artery. Ann. of Surg., 76:788, 1922.

Danzis, Max: Arterial Embolectomy. Ann. of Surg., 87:667, May, 1928.

Dickinson, A. M.: Embolectomy; report of a case. Arch. of Surg., 10:991-995, May, 1925.

Dschanelidze, J. J., and Ogloblina, S. W.: Embolectomy. Arch. für klin. Chir., 149:55-74, Dec., 1927.

Garin, H.: Brachial embolectomy. Rev. méd. de la Suisse Rom., 47:562-564, July 25, 1927.

Given, J. B., Jr.: Surgical aspects of embolism. Surg. Clin. North America, 7:857-861, Aug., 1927.

Gordon-Watson, C.: Case of Embolectomy. Brit. Med. Jour., 1:1032, 1926.

Haggstrom, P.: Three cases of embolectomy. Upsala Läkaref. Förh., 28:107, 1922-23.

Hartley, J. N. J.: Surgical treatment of embolism of the extremities. Edin. Med. Jour., N. S., 30:408, 1923.

Henney, C. W., Snyder, K. A., and Hoyer, A. A.: Embolectomy; successful removal of embolus from first part of subclavian artery. Jour. Amer. Med. Assn., 84:1566, 1925.

Jefferson, G.: Report of a successful case of embolectomy with a review of the literature. British Med. Jour., 2:985, 1925.

Jentzer, and Bonnet, P.: Embolectomie. Lyon chirurg., 23:618, 1926.

Key, E.: Uber Embolectomi als Behandlungsmethode bei embolischen Zirculationsstörungen der Extremitäten. Acta Chir. Scandin., 54:339, 1921-22.

Key, E.: Embolectomy in the treatment of circulatory disturbances in the extremities. Surg., Gynec. and Obstet., 20:1, 1923.

Key, E.: Embolectomy in embolic disturbances of extremities. Zentralbl. f. Chir., 54:2190, 1927.

Lahey, F. H.: Treatment of emboli in peripheral vessels. Surg. Clin. North America, 6:651, 1926.

Loreti, M.: Embolism and embolectomy. Gior. d. med. prat., 10:48-55, March, 1928; 79-87, April, 1928.

Lundberg, S.: Case of Embolectomy. Acta Chir. Scandin., 56:412, 1923-24.

Mason, R. L., and Hurxthal, L. M.: Femoral embolectomy. New England Jour. Med., 198:277-280, March 29, 1928.

MacDougall, J. G.: Arteriotomy for embolus obstructing circulation in extremity. Canad. Med. Assn. Jour., 16:265, 1926.

Michaëlsson, E.: Über 3 Fälle von arterieller Embolektomie. Acta. Chir. Scandin., 55:427, 1922-23.

Michaëlsson, E.: Ein Fall von geglückter Embolektomie. Acta Chir. Scandin., 56:431, 1923-24.

Most, N. G.: Surgical removal of arterial embolus in impending gangrene of extremity; its indication and prognosis. Deutsch. med. Wchnschr., 5:1501, 1924.

Mosny and Dumont: Bull. de l'Acad. de med., 66:358, 1911.

Moure, P.: Embolectomy. Bull. et mém. Soc. nat. de chir., 53:301, March 12, 1927.

Nystrom, G.: Prognosis and methods of embolectomy. Acta Chir. Scandin., 60:229, 1926.

Odelberg, A.: Case of embolus in the popliteal artery. Acta Chir. Scandin., 59:540, 1925-26.

Olivecrona: Second successful embolectomy in the same patient. Acta Chir. Scandin., 57:411, 1924.

Pemberton, John de J.: Embolectomy. Ann. of Surg., 87:652, May, 1928.

Perman, E.: Case of Embolectomy. Acta Chir. Scandin., 56: 555, 1923-24.

Remijnse, J.: Case of embolectomy. Nederl. Tijdschr. v. Geneesk., 1:1374-1379, March 17, 1928.

Sencert, L., and Blum, P.: Un cas d'arteriotomie pour obstruction embolique de l'axillaire suivre de guerison complete et definitive. Bull. de l'Acad. de méd., Paris, 88, 3 s.:84, 1922.

Sencert, L., and Blum, P.: Surgical removal of embolism. Presse méd., 30:853, 1922.

Sencert, L.: Les embolies arterielles des membres et leur traitement chirurgical. Rev. de chir., 61:623, 1923.

Stein, A.: Gangrene of extremities following gynecologic operations and puerperium, with remarks on embolectomy. Amer. Jour. Obstet. and Gynec., 9:595, 1923.

Söderlung, G.: Two cases of embolectomy. Acta Chir. Scandin., 59:225, 1925.

A BACTERIOLOGICAL STUDY OF A GROUP OF DISEASED GALL BLADDERS*

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THE present study was undertaken to ascertain something of the etiology and pathology of gall bladder disease and to determine efficacious modes of treatment for cases presenting this condition. McClure[1], in a series of publications on the clinical and chemical aspects of the problem, has drawn some striking conclusions and outlined some promising aids both for diagnosis and treatment. In the current paper is presented the result of the bacteriological studies; the histological findings will appear in a subsequent publication.

There is no intent to dwell at length upon the history of the subject, but a few introductory words seem imperative. From time to time various authors, here and abroad, have reported similar research. Due to obvious diversities in material, methods of approach and personalities of the investigators the end results show as great a multiplicity of theories as there are reported studies. In Table I we have collected some of the more pertinent findings.

This study is based upon the bacteriological and histopathological examination of 210 gall bladders removed during the course of the routine surgical work of the Massachusetts Homoeopathic Hospital. These were removed under the usual aseptic surgical conditions and dropped by the surgeon into large, sterile petri dishes, which were sealed with adhesive tape and immediately transported to the laboratory. Here the seal was broken, cultures taken from the gall bladders and histological sections cut from three points. If stones were present, from one to three of them were also cultured.

The first culture was taken from the serosa opposite the surface recently dissected from the liver. Next, a point approximately a centimeter away from this area was seared and the serosa was picked up and incised with sterile instruments. Through this opening with a fresh set of sterile instruments, a burrow was made deep into the muscularis, well beyond the seared area and in a direction still away from the dissected surface. At the distal end of such a burrow a drop or two of serum will accumulate; from this a culture was made. Next, the seared wall was incised with a fresh sterile scalpel and a culture was made from the bile. Stones were held in a pair of forceps and flamed until much of the exterior was burned or melted off. They were then split and their central portion scraped into a finely granular mass, with which the culture media were directly inoculated.

The cultures taken were planted both aërobically and anaërobically on hormone broth and agar having a pH value varying bewteen 7.2 and 7.6. Best growth was obtained on a semi-solid, synthetic medium suggested by Enlows[2]. It is easily prepared, is very clear and allows a wide range of fermentation tests because of its sugar free base. The fermentation substrates were usually added in concentration of 0.5 per cent. of the following formula:—

H_2O	1800 cc.
PEPTONE	10 gm.
Na_2HPO_4	14.5 "
KH_2PO_4	1.4 "
AGAR	2.5 "

Strains were maintained on blood agar plates till properly classified and then kept in stock in the semi-solid medium. Shönfeld's[3] methods of classification were used in differentiating the enterococcus group. Routine laboratory procedures were employed for classifying the remaining groups of organisms.

Of the 210 cases, 16 per cent. were males, and 83 per cent. females. Of the latter, 80 per cent. were married, but in all instances a history of pregnancy was not ascertained. The average age of the group was slightly over 40, the youngest being represented by two cases of acute cholecystitis accompanying scarlet fever in children of five and eight years, respectively.

Cultures from the serosa were almost entirely negative. In the few instances in which they were positive, the organisms recovered were of such a nature as to be considered frank contaminants or corresponded exactly in type with organisms recovered from massive infections of the wall. The relative frequency of occurrence of various types of organisms in the gall bladder wall and its contents are summarized in Table II.

To these statistics we may add the following notations. Fourteen strains of streptococci were isolated in pure culture. From their sugar reaction, five of these belong in the enterococcus group; six were of the beta and three of the alpha hemolytic type. The two instances above mentioned as sequelae of scarlet fever are from a larger unpublished series of similar cases encountered by Dr. Clifford Harvey[4]. A beta hemolytic streptococcus was isolated from the wall of one. The other was not cultured, but shows Gram positive cocci in short chains in the wall.

The two cases from which B. typhosus was isolated are interesting in the light of the fact that in neither was there any history or knowledge of ever having had the disease. In all probability the stone infection occurred during a mild and unrecognized attack. Plausibly enough, the later acute process present in the wall and bile of one case may have occurred

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†For record and address of author see "This Week's Issue," page 339.

TABLE I*

TABULAR REVIEW OF 3575 CASES OF CHOLECYSTITIS WITH PARTICULAR NOTE OF THE BACTERIOLOGICAL FINDINGS

Author	Number Cases Reported	Number Acute Cases	Positive Cultures in Acute Cases	Number Chronic Cases	Positive Cultures in Chronic Cases	Stones Present in	Stones Giving Positive Cultures	Walls Giving Positive Cultures	Biles Giving Positive Cultures	Predominating Organisms in Order of Frequency
Branch	210	57	42	153	11	94	27	53		B. coli - Staphylococci - Streptococci
(28) Brown	70	20	15	50	21			36		Streptococci - B. coli
(29) Burden	112	Summary: Cholecystitis is not usually the result of an acute process, but rather is a mild infection slowly affecting the different layers of the gall bladder. Chronicity is favored by the anatomy and histology of the organ which predisposes to stasis and obstruction.								
(20) Deaver	903					451				
(23) Kelley	240							113		B. coli - B. typhosus - Staphylococcus aureus
(19) Denton	403	Summary: Failure to demonstrate lesions primarily bacterial in origin leads the author to conclude that factors other than infection (mechanical and circulatory) are necessary for the explanation of the majority of the lesions commonly observed in the gall bladder.				188	In only 4 of 94 specially stained paraffin sections were organisms found and these were B. coli or a coarse, Grampositive bacillus.			B. coli
(13) Drennan	100								19	B. coli - Staphylococci - Streptococci
(18) Feinblatt	400	Summary: A pathological study leads one to believe that the rôle of infection in the causation of cholecystitis has been greatly overestimated while the importance of metabolic and mechanical factors has not received due consideration.				240	Of 20 surgical cases of empyema of the gall bladder containing thick pus, 8 gave positive cultures in which B. coli predominated.			B. coli
(24) Illingworth	100	12	10	88	52	62	7	62	40	Streptococci - B. coli - Staphylococci. 15 cystic glands examined and 6 positive. 3 Streptococci - 3 B. coli
(14) Johnson	100	20	13	78	18	62	16	31	32	B. coli - Staphylococci - Streptococci
(30) Judd	200					107	of 67 examined 24	98	of 197 examined 28	Streptococci - B. coli - Staphylococci
(31) Moynihan	81							30	25	
(17,33) Rosenow	76						of 92 examined 57	of 64 examined 51	of 55 examined 30	Streptococci - B. coli
(32) Rovsing	530					530	216			
(25) Wilkie	50							6	6	Streptococci - B. coli Obtained growth from 45 cystic glands of which 43 were Streptococci

*See explanation at end of bibliography.

as a reinfection from one of the stones. Among other interpretations derived from the work of Meyer, Neilson and Feusier[5], who have recorded many valuable points in regard to gall bladder infection, especially by the B. typhosus group, we find that these organisms may still be viable after two years in such vital organs as the lungs, liver, bone marrow and intestine. On the other hand, they state that the elimination of B. typhosus in the feces is almost invariably associated with gall bladder or bile passage infection. Rolleston[6] and Osler[7] both admit the presence of organisms in the blood during the course of the disease, yet neither found cholecystitis to be a very constant accompaniment; in fact Osler noted only 19 such cases out of a series of 1500 typhoid patients. Throughout the bacteriological investigations abstracted in Table 1, the infrequency of B. typhosus, as an infecting organism, was notable. Nevertheless, the relationship should be remembered because, from the standpoint of potential carriers, it is unquestionably important. Crowell[8], Schöbl[9], and others have shown it to be a distinct factor in cholera carriers. Many clinicians in metropolitan areas have first-hand knowledge of cases in which typhoid carriers have been cured by extirpation of this nidus of infection. Our case in which wall, bile and stone were all infected, was one in which operative interference eliminated an almost certain carrier.

TABLE II

FREQUENCY OF OCCURRENCE OF ORGANISMS RECOVERED*

Source	Number Examined	Number Positive Cultures	B. Coli	Staphylococci	Streptococci	B. dysenteriae	B. Welchii	Mixed Cultures	B. typhosus	Unidentified Organisms
Wall	210	53	49	17	11	4	8	6	2	4
Bile	210.	40	50	18	15	3	5	5	3	3
Stone	94	27	52	19	7	4	7	-	7	4

*Tabulated in per cents., calculated to the nearest whole number.

In 12 cases we attempted animal inoculation with a view to recovery and selective determination of the organism. Our method of procedure consisted of intravenous injections, in graduated doses, of living organisms, repeated every three days over a period of two weeks. At the end of this period the animals were autopsied. The organisms used on the first injection were never older than the second generation. With the exception of those dying from acute infections, the animals showed very few signs of distress or illness. Six of the rabbits died of intercurrent causes. Of the remainder, two inoculated respectively with Staphylococcus aureus and a fecal streptococcus did not return the organism injected. At autopsy, the four remaining rabbits showed gall bladder involvement out of all proportion to the other lesions present. One animal injected with B. coli showed no other lesions. The blood from two injected with Streptococcus haemolyticus and B. typhosus gave positive cultures, while the two injected with B. typhosus and B. dysenteriae showed a well defined enteritis. We should like to attach some importance to our findings but feel that, aside from corresponding in a measure with the experience of others, notably Rosenow[10] and Meyer[11], our work along these lines has been too meager to offer a positive record.

Almost without exception we have been able accurately to prejudge the presence or absence or organisms in the bile by its gross appearance and physical properties. Neilson and Meyer[12] find that the vigor of bacterial growth in cystic bile is noteworthy and that complete suspension of growth occurs only at a pH which in all probability never occurs in the human body. On the other hand they admit that concentration is an important factor. Drennan[13] and Johnson[14] have demonstrated that most organisms will not grow in bile, the concentration of the salts of which is over 70 per cent. of normal. Generally speaking, below this point bacterial growth is in inverse ratio to bile concentration. In but few cases did we find bile that was thin and of low index that did not contain organisms. Rous[15] and Boyd[16] have shown that one of the most important functions of the gall bladder is that of materially concentrating the bile. We are thoroughly convinced that when thinned by inflammatory exudates or, perhaps, even through failure of normal physiological concentration, the bile is prone to become a culture medium for organisms. This normal physiological reaction is undoubtedly responsible for the failure of Rosenow[17] to produce a cholecystitis by directly inoculating the bile with organisms, that, when given intravenously, did produce positive lesions in that organ, without the presence of secondary factors, such as stasis or vascular changes. Hence we may assume that in a normal organ, one of whose chief activities is to concentrate bile to 1/6 of its original volume, primary infection of its contents is bound to be rare. The above findings have been substantiated in a long series of autopsies in which we have noted a close relationship between thinning of the bile and the existence of pathology in the wall.

What constitutes an infected gall bladder? Obviously, one in which bacteria are present, yet is that sufficient? It seems as though we

were assuming too much to say that an organism recovered from a chronic cholecystitis is responsible for that chronicity in the face of the freely anastomosing lymphatics connecting the gall bladder wall with other organs, unless we can establish a definite relationship between that organism and a focus of marked chronic inflammation. Or, on finding an organism present in an acutely inflamed bladder, how can we be sure that it is the original instigator of the trouble? As Meyer[5] has pointed out, some of Rosenow's streptococcic infections are due to secondary invaders and almost all authors have reported numbers of mixed cultures. What part of the organ must give a growth to make a diagnosis? Unquestionably, cultures from the wall are most reliable. The bile is rarely infected unless the wall shows some phase of an acute inflammation. Many stones are infected, yet, in all probability, a very small percentage of them are ever responsible for reinfecting the wall. As for the relative frequency of types of cholecystitis from which we recover organisms, the disconcerting consistency of positive cultures from the acute cases is only equalled by the persistent lack of growth from the chronic cases.

In Table III we present our own findings as regards the prevalence of gall bladder infection, while in the following paragraph we have summarized the figures of the various authors, as compiled in Table I.

TABLE III

Occurrence of Infection in Acute and Chronic Cases

Source	Acute Cases	Per cent. Positive Cultures	Chronic Cases	Per cent. Positive Cultures
Wall	57	74	153	7
Bile	57	60	153	4
Stone	15	60	79	23

Of 875 walls examined bacteriologically, including acute and chronic cases, 348, or 40 per cent., gave positive growth. Now if we take the figures of authors who have separated acute from chronic cases, namely Illingworth, Johnson and our own, we find the following: of 89 acute cases cultured, 65, or 73 per cent., were positive; while of 319 chronic cases, only 81, or 25 per cent., gave positive growth. Deleting Illingworth's figures, which are constantly high, from this last group, we have 231 cases of which 29 or 12.5 per cent., gave growth on culture. Of 893 bile cultures, 220, or 25 per cent., were positive. Examination of 868 stones gave positive growth in 349 cases, or 40 per cent. Rovsing's[32] figures, which are based on 530 cases, must of course dominate our results, but when we exclude his figures we have 338 remaining, of which, happily, 133, or 39 per cent., are positive.

In the face of these figures, we must not lose sight of the fact that the consensus of opinion willingly concedes that mechanical factors, such as stasis, pressure, vascular changes, immobility caused by old adhesions and the irritation caused by stones, as well as chemical and toxic irritants, still initiate a great many cases of acute cholecystitis. On the other hand, we feel that such extreme reports as those of Feinblatt[18] and Denton[19] tend to create an erroneous impression. They report over 800 cases from which they draw inferences decidedly opposed to a theory of sustained infection. Unfortunately Deaver[20], in a clinical review of over 900 cases, failed to note the presence or absence of infection, although he did find evidence of accompanying disease of the liver in 6 per cent. of his cases. This infrequent occurrence of liver involvement is in accord with Martin's[21] theories, but is at marked variance with the extensive work of Graham[22] and his school. In a series of 240 cases from Deaver's clinic, Kelly[23] found organisms present in 47 per cent., as recorded in Table I.

What type of organism predominates in infections of the gall bladder? Graham, in his recent book, draws conclusions based upon some of the work represented in Table I, conclusions which are apparently substantiated by our further and somewhat more exhaustive review of the subject. We may conclude with some confidence that streptococci and B. coli are most frequently isolated from infected gall bladders with the staphylococcus easily in third place and the remainder of the organisms relegated to an occasional appearance.

The relatively frequent appearance of B. Welchii, as noted by several authors, is not unfamiliar to those who are privileged to look over much autopsy material. The organism is indigenous to the area drained by the portal system, but apparently its activity is held in abeyance by normal living tissues. After death in bodies poorly preserved, particularly in the summer months, B. Welchii rapidly develops and extensively damages tissues between the time of death and fixation. In some instances it grows to such an extent that the ensuing myriad of small gas bubbles give the liver all the appearance of a rubber sponge, the "foamy liver". This being the case, it is not strange that we encounter this organism in our cultures so frequently.

Rosenow[17] found that the organisms rapidly disappeared from tissues. In our experience, Gram stains on even very fresh tissue produced astonishingly poor results. Denton[19] experienced similar difficulty in staining organisms in the gall bladder and allowed this deficiency to color his conclusions.

Examination of the "cystic gland" to deter-

mine existence of an infected gall bladder is of doubted value. Illingworth[24] and Wilkie[25] attach great importance to this procedure, maintaining that in all gall bladder diseases the gland is found to be enlarged and, in the majority of instances, infected with streptococci. Embryologically and histologically we find lymph nodes to be parts of an extensively and intimately anastomosing system. Practical experience strongly substantiates and, if anything, tends to over-emphasize this close relationship. It is then logical to assume that this node, situated at the neck of the gall bladder, is only one unit of the lymphatic drainage of that closely associated quintet, the liver, gall bladder, duodenum, stomach and pancreas. This being the case, it is hard to believe that all organisms found there must have come from the gall bladder. Histologists have long recognized a lymphatic connection between the liver and gall bladder. Sudler[26] and, more recently, Kodama[27] have emphasized the fact, popularized by Graham, that the liver, the filter bed of the entire portal system, is intimately connected with the gall bladder by its freely anastomosing and relatively large lymphatic channels.

The mode of infection is perhaps considered more logically in a histological, rather than a bacteriological, review of the subject. It is sufficient here, that of the four possible routes of infection, the hematogenous, the lymphogenous, the ascending or biliary, and that of direct continuity, the hematogenous route is favored by the majority of authors, while the lymphatic route is considered next in importance.

CONCLUSIONS

1. In chronic cholecystitis the gall bladder is infected in approximately 12 per cent. of the cases.
2. In acute cholecystitis the gall bladder is infected in approximately 75 per cent. of the cases.
3. Approximately 40 per cent. of all gall stones are infected.
4. Bile in which the bile salts have a normal or high concentration has a marked inhibitory effect on bacterial growth.
5. The predominating organisms recovered from infected gall bladders in the order of frequency are B. coli, streptococci and staphylococci.
6. The organism recovered from a case of acute cholecystitis is not necessarily the primary etiological factor responsible for the development of the acute lesion.
7. Organisms recovered from the "cystic gland" are not a fair criterion on which to base an assumption of existing infection in the gall bladder.

BIBLIOGRAPHY

1 McClure, C. W.: Am. Jour. Med. Sci. 176: 309, (Sept.) 1928.
2 Enlows, E. M. A.: Public Health Reports. 38: 2129, (Sept.) 1923.
3 Schönfeld, H.: Centralbl. f. Bakteriol. 1. Abt., 99: 388, 1926.
4 Harvey, C. D.: Unpublished work on acute cholecystitis in children.
5 Meyer, K. F., Neilson, N. M., and Feusier, M. L.: Jour. Infect. Dis. 28: 408, 1921.
6 Rolleston, H.: Lancet. 208: 1207, (June) 1925.
7 Osler and McCrae: Principles and Practice of Medicine,—9th Ed., N. Y. & Lond., Appleton & Co., 1920, p. 24.
8 Crowell, B. C.: Philippine Jour. Sci. 12: Sec. B, 85, 1915.
9 Schöbl, O.: Philippine Jour. Sci. 10: Sec. B, 11, 1915.
10 Rosenow, E. C.: Surg., Gyn. and Obst. 33: 19, 1921.
11 Meyer, K. F., Neilson, N. M., and Feusier, M. L.: Jour. Infect. Dis. 28: 456, 1921.
12 Neilson, N. M., and Meyer, K. F.: Ibid. 542.
13 Drennan, J. G.: Ann. Surg. 76: 482, 1922.
14 Johnson, W. O.: Am. Jour. Med. Sci. 170: 181, 1925.
15 Rous and McMaster: Jour. Exp. Med. 34: 63, (July) 1921.
16 Boyd, Wm.: Brit. Jour. Surg. 10: 337, 1923.
17 Rosenow, E. C.: Jour. Infect. Dis. 19: 527, 1916.
18 Feinblatt, H. M.: N. E. Jour. Med. 199: 1073, (Nov.) 1928.
19 Denton, J.: Arch. Surg. 14: 1, (Jan.) 1927.
20 Deaver, J. B., and Bortz, E. L.: Jour. A. M. A. 88: 619, (Feb.) 1927.
21 Martin, W.: Ann. Surg. 85: 535, 1927.
22 Graham, Cole, Copher, and Moore: Diseases of Gall Bladder and Bile Ducts. Lea & Febiger, 1928, p. 119.
23 Kelly: Quoted by Stengel, A., and Kern, R. A., in Nelson's Loose-Leaf Living Med.—Vol. 5, p. 505.
24 Illingworth, C. F. W.: Brit. Jour. Surg. 15: 221, (Oct.) 1927.
25 Wilkie, A. L.: Brit. Jour. Surg. 15: 450, 1928.
26 Sudler, M. T.: Bull. Johns Hopkins Hosp. 12: 126, 1901.
27 Kodama, S.: Surg., Gyn. and Obst. 43: 140, 1926.
28 Brown, R. O.: Arch. Int. Med. 23: 185, 1919.
29 Burden, V. G.: Ann. Surg. 85: 239, (Feb.) 1927.
30 Judd, Mentzer and Parkhill: Am. Jour. Med. Sci. 173: 16, (Jan.) 1927.
31 Moynihan, B.: Brit. Med. Jour. 1: 1, (Jan.) 1928.
32 Rovsing, T.: Acta Chir. Scandinav. 56: 103, 1923.
33 Rosenow, E. C.: Jour. A. M. A. 63: 1835, (Nov.) 1914.

Reference numbers above names in Table I.

MEDICAL PROGRESS

PROGRESS IN THE STUDY OF CARDIOVASCULAR DISEASE IN 1928

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IT has been customary for the NEW ENGLAND JOURNAL OF MEDICINE in the past six years to publish a comprehensive survey of the literature pertaining to cardiovascular disease. With the tremendous increase in material during these years, the review has proportionately grown in length. An attempt will be made in the present summary to limit the report to references to new material. It will, therefore, be impossible to include general or discursive papers or more than a few unusual case reports and there will be an intentional omission of many valuable papers which, in the reviewer's opinion, do not add new data nor methods of approach. Progress in the subject in the past year seems chiefly to have been concerned with the anatomy of the heart (capillaries and lymphatics), attempts at blood flow and velocity determinations, the relation of some dietary deficiency diseases to the heart, the etiology of rheumatic heart disease, the hormonal influences upon cardiac rhythm, the testing of some of the newer drugs, and the therapeutic advances in the problems of hypertension and angina pectoris. In reviewing such progress, one must recall that 1928 marked the 300th anniversary of that greatest advance in the study of cardiovascular dynamics—the publication of William Harvey's "Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus". This event was celebrated in England in one manner by the recording cinematographically of the experiments of Harvey reproduced by Sir Thomas Lewis and H. H. Dale.

I. ANATOMY AND PHYSIOLOGY

A careful correlation between heart weight and body weight and heart weight and age has been completed by *Smith* at the Mayo Clinic from autopsies of 1000 cases with normal hearts. He concludes that "1. The average weight of the adult male heart is 294 gm., the average weight of the adult female heart is 250 gm.; 2. There is a definite correlation between weight of the heart and weight of the body. The ratio is 0.43 per cent. for male and 0.40 per cent. for females. The ratio is slightly higher in thin persons and lower in obese persons. This coefficient is not so accurate for body weights of less than 45 kg. (100 pounds) and more than 94.5 kg. (210 pounds). 3. The weight of the heart may be calculated from the weight of the body with an error varying from 8 to 10 per cent. 4. The weight of the heart does not increase with age, irrespective of the weight of the body. The weight of the heart increases with increase in the weight of the body."

In the vascular anatomy of the heart the work of *Campbell* with stereoscopic radiography of injected coronaries in 92 hearts should be mentioned. He was able to show narrowing of the ostia in early coronary disease and in some cases rich anastomoses between right and left arteries. *Kugel* has described such an anastomosis by the arteria anastomatica auricularis magna, a large vessel in the auricular wall. Its distribution suggests, moreover, a relationship to pathology at the mitral and aortic valves and root of the aorta.

Ritter, Gross and *Kugel* report a study showing blood vessels present in the heart valves in only 14 normal cases among 700 human hearts studied. 109 cases with inflammatory lesions of the heart showed vascularization of the aortic leaflet of the mitral valve.

Wearn continuing his work has described the capillary connections of the heart. He found them to be very numerous, averaging one for each ventricular or papillary muscle fiber and less in the auricle and Purkinje system. This indicates a supply twice as great as Krogh was able to show in skeletal muscle. Capillaries were not found constantly in the valves. Wearn has also further elaborated the rôle of the Thebesian vessels in intracardiac circulation, stressing their connection with the coronary arteries and veins and the heart chambers and their importance in the mechanics of compensatory circulation after coronary occlusion, even to the extent of assuming the responsibility for cardiac nutrition after complete closure of both coronary arteries.

Kampmeier has studied the lymphatic supply of the heart especially its embryology. It arises from the mediastinal lymphatics and becomes highly complex over the ventricles and less over the auricles. Lymph flow would appear to be continuous and from within toward the outside of the heart and constitutes a drainage system for "the products of cellular metabolism not selected by the venous capillaries".

The connections of the sympathetic system with the heart are of increasing importance, especially in relation to operative procedures for the relief of angina pectoris. Much im-

*For record and address of author see "This Week's Issue," page 339.

mediate interest is centered on the stellate ganglion. *Ionescu, Enachescu* and *Teitel* have dissected out a new group of sympathetic fibers running to the heart below the level of the stellate ganglion and usually originating from the 2nd to the 5th thoracic ganglia. There was often considerable anastomosis between themselves and with the branches to the stellate, vagus and recurrent nerves. In some cases no anastomosis occurred with other groups and in others there were no connections with the other side of the body or with inferior or median cardiac nerves. The left side of the heart was more freely supplied, since the right nerves more frequently crossed over. The terminations could be traced to the auricles and often even to the ventricles. It is to be concluded that bilateral stellate ganglionectomy does not deprive the heart of accelerators.

Among the physiological papers of interest mention should be made of those of *Blumgart* and *Weiss* on pulmonary circulation time in normal patients and those with circulatory disease. They calculated that the average amount of blood in the lungs was 984 cc. or approximately 21 per cent. of the total blood volume. "The quantity varies considerably in different individuals. The results indicate that the pulmonary circulation time is an index of the mean time consumed by the blood flow through the lungs. The observations suggest that in normal persons the available pulmonary pathways are approximately equal. Normal variations in the pulmonary circulation time are not related to corresponding normal variations in the minute volume blood flow through the lungs."

Chang and *Harrop* report a method of measuring circulating blood volume in man by blood determination of inhaled carbon monoxide. They claim an error of not more than 5 per cent.

Thompson, Thompson, and *Dailey* demonstrate a loss of about 11 per cent. of total plasma volume in the standing still position due to an increase in capillary pressure most marked in the legs. This occurs in 20-30 minutes and is made up in about the same time in recumbency.

Among some 20 papers on the subject of a cardiac activating substance derived from the heart itself may be mentioned the contribution of *Haberlandt*. He prepares his heart hormone by immersing the sinus venosus and great veins of two frogs (Rena Esculenta) in 1 c.c. of Ringer's solution. The extract may be equally obtained from the sinus node or the A-V bundle. When perfused through the isolated frog's ventricle by Straub's cannula, acceleration and increased amplitude of the beat will occur if the heart is hypo-dynamic or if it has stopped, pulsations will be initiated.

The extract employed differed from the accelerator material described by Loewi in not being destroyed by fluorescence or ultra-violet light. It does not resemble adrenalin as it produces vasodilation rather than vasoconstriction. The hormone may be extracted with alcohol, less easily with chloroform and not at all with ether. The aqueous extract seems to be the more suitable. The hormone is heat resistant and is absorbed by charcoal.

Similar work done on warm blooded animals shows that an extract prepared in Locke's solution from the right auricle in dogs produced an increase in the number and amplitude of beats in rabbits' hearts.

The hormone does not seem to be genus specific and may be obtained from the entire conducting system of the heart. The author quotes the work of Ryland and De Moor, Kemal, Mouchet, and others, who have worked on similar lines.

Lewis and *Haynal* in discussing their observations relating to the tone of the minute vessels of the human skin, disagree with the statements by Krogh and by Krogh and Rehberg that "a definite change in the blood colour of an organ always implies a change in the state of contraction of its capillaries" and that "vivid colour reactions like the flare must necessarily involve an acute relaxation of the capillaries and especially of the vessels." Lewis and Haynal conclude as follows:

"1. No satisfactory evidence that the reflex flare can appear on skin to which the circulation has been stopped has yet been obtained. The so-called ghostlike flare is in part illusory and in part due to a natural mottling of the skin.

2. In attempting to estimate the pressure in the minute vessels of the skin by noting changes of colour that occur when pneumatic pressures are thrown upon the skin, such an index as "slight" or "distinct" paling is inadmissable. The amount of paling that will occur when the correct external pressure is used chiefly depends upon the original amount of blood in the cutaneous vessels.

3. The most satisfactory colour index in such tests is an end point of colour. If in congested skins, natural skin colour is taken as the end point, this index will provide minimal values for the pressures in the vessels that give colour to the skin.

4. The minimal values for bright histamine flares are about 50 to 60 mms. Hg."

II. Etiology and Pathology

A. General

White and *Jones* have published an etiological survey of heart disease as seen in 3000 cases in New England divided equally among those seen in hospital clinics, general practice, and consultation work. Their findings were as follows: "Four-fifths (80.7 per cent.) had organic heart disease, if one includes cases with uncomplicated angina pectoris (2.6 per cent.) and uncomplicated auricular fibrillation (1.0 per cent.). One-

fifth (19.3 per cent.) had relatively unimportant functional circulatory abnormalities.

"In the group of 2421 cases of organic heart disease, including the patients with uncomplicated angina pectoris (77) and uncomplicated auricular fibrillation (30), the etiological factors apparently present, both alone and uncomplicated, were found to be as follows in the order of frequency: a) "rheumatic"—956 cases or 39.5 per cent.; b) arteriosclerotic—364 cases or 35.7 per cent.; c) hypertensive, 708 cases or 29.2 per cent. (hypertensive or arteriosclerotic or both, 1165 cases or 48.1 per cent.); d) angina pectoris, 353 cases or 14.6 per cent.; e) syphilitic, 95 cases or 3.9 per cent.; f) coronary occlusion, 71 cases or 2.9 plus per cent.; g) hyperthyroid, 68 cases or 2.9 per cent.; h) subacute bacterial endocarditis, 45 cases or 1.9 per cent.; i) congenital, 37 cases or 1.5 per cent.; j) miscellaneous, 51 cases or 2.1 per cent.; k) unknown (including the 30 cases of uncomplicated auricular fibrillation) 82 cases or 3.4 per cent. Frequently two and sometimes three of these etiological factors appeared to be combined in the same case.

"In the group of 579 cases with relatively unimportant functional circulatory abnormalities and without evidence of heart disease the various disturbances were represented, alone or in combination, as follows: a) effort syndrome, 303 cases or 52.3 per cent.; b) functional systolic murmurs, 114 cases or 19.7 per cent.; c) premature contractions, 82 cases or 14.2 per cent.; d) paroxysmal tachycardia, 79 cases or 13.6 per cent., and e) sinus arrhythmia (marked) 3 cases or 0.5 per cent.

"Auricular fibrillation occurred altogether in 376 cases of the 3000, thirty times apparently uncomplicated. In 67 patients it was paroxysmal and in 309 permanent in type. Auricular flutter was found in only 6 patients.

"Auriculoventricular heart block was found in 59 patients and intraventricular block in 52, both undoubtedly underestimated.

"Alternation of the pulse was noted in only 40 patients.

"In the present study, patients with organic heart disease were more common in the hospital group than in private practice. Thus uncomplicated effort syndrome was found in 207 cases in private consultation, in 60 cases in general practice, and in 35 cases in the hospital group. Also angina pectoris was found much more frequently in private practice, being recorded in 141 cases of the general practice series . . . and in 83 cases in the hospital. On the other hand, rheumatic heart disease was much more common in the hospital and dispensary group than in private practice (474 in the former and 282 and 200 respectively in the latter). Syphilitic etiology was found in 43 cases of the hospital group and in only 23 cases in private consultation."

Wilson, Lingg and *Croxford's* review of 500 cases in young people observed at a heart clinic in the past ten years, is a valuable contribution to clinical study. The data are too extensive to report. It is interesting that they found 11.2 per cent. of congenital defects. Three-fourths of 413 children with a rheumatic history developed organic heart disease. The peak of the mortality curve was at 11 to 14 years of age.

Coffen and *Carey* report the findings in 3000 school children in Seattle. 191 had heart murmurs but only 15 had rheumatic heart disease. They were especially struck by the frequent finding of the basal systolic murmur, usually at the pulmonic area. This murmur, which they consider of little significance, was louder after exercise and heard equally well at the pulmonic and mitral areas or loudest at the pulmonic area or well heard at the aortic area.

B. CONGENITAL

Rösler has reported a Roentgen ray study of 68 cases of congenital defects of the heart or great vessels so diagnosed clinically, a few with post mortem confirmation. He reports that 58 (85.3 per cent.) of these cases showed positive Roentgen ray findings in heart or vessels, 8 (11.7 per cent.) negative, and 2 doubtful. Among the cases with positive findings, Roentgen ray changes were found in the heart alone in 20 per cent., in the great vessels alone in 15.5 per cent., chiefly in the heart in 84.4 per cent., chiefly in the aorta in 18.9 per cent., and chiefly in the pulmonic artery in 62 per cent. In 51.4 per cent. of all the cases, or 60.3 per cent. of the positive cases, the Roentgen ray findings were of value in establishing the diagnosis and in a few cases were of paramount importance. Yet in some important cases, for example in 25 per cent. of the cases of Morbus Coeruleus in the present series, the heart and great vessel Roentgen ray findings were completely negative.

Maude Abbott has collected 200 cases of coarctation of the aorta of the adult type and discusses the diagnosis and prognosis. Two lived over the age of 70 but the decade with highest mortality was 20 to 30 years of age. "The retardation and diminution or even absence to the palpating finger of the femoral pulse . . . in combination with evidence, wheresoever obtained, of dilated pulsating vessels or arterial murmurs in the upper part of the body is pathognomic of coarctation. It is, however, not constant."

Blackford reported from the Mayo Clinic, 5 cases of coarctation of the aorta with autopsy findings and 7 other probable cases. He concludes: "Narrowing or obliteration of the aorta in the region of the mouth of the ductus arteriosus or its vestige is believed to be due to absence, atrophy or imperfect development of the left fourth branchial arch. Syphilis is not an etiologic factor.

"The division into the infantile type, in which the constriction is proximal to the ductus, and

the adult type, in which it is at or just distal to it, though not precise, is convenient morphologically and clinically.

"Coarctation has been found in 127 necropsies on infants and young children. The clinical diagnosis in such cases is of little or no actual importance because coarctation of the infantile type is rapidly fatal, or, if of the adult type, hardly a factor in causing death.

"Coarctation has been found in at least 196 necropsies on older persons. More than 40 per cent. of these were from 16 to 30 years of age, and more than 70 per cent. died from cardiovascular causes. In addition, coarctation in thirty-five cases was overshadowed by other cardiovascular defects of developmental origin.

"Coarctation has been diagnosed clinically in seventy-eight cases and corroborated at necropsy in twenty-one of these. The diagnosis is often suggested by an unusually high pulse pressure or by a loud systolic murmur in the left interscapular space, and confirmed by the presence of pulsating superficial arteries over the thorax and the diminution or absence of pulsation in the abdominal aorta and femoral arteries.

"Coarctation once diagnosed indicates the removal of possible foci of infection and especially if the patient is a robust, athletic young man, a regimen of limited physical activity."

Emerson and *Green* have discussed idiopathic hypertrophy of the heart in infants with 11 new cases. Cardiac enlargement with dyspnoea and cyanosis were the main findings. The oldest case was 28 months of age. They suggested as an etiology, a congenital narrowing of the capillary bed.

Reinberg and *Mandelstam* analyze the results of clinical, roentgenologic and electrocardiographic investigations of thirty-seven cases of dextrocardia. Twenty-two of these were cases of total transposition of viscera, five of congenital isolated dextrocardia and ten of acquired dextroposition of the heart. The frequency of total transposition in their material was one in 1,500 roentgenologic examinations. They distinguish four types of dextrocardia: (1) Dextrocardia in the presence of total transposition of viscera. This type gives a clear-cut, characteristic roentgenogram and a reversed electrocardiogram. (2) Isolated congenital dextrocardia with inversion of cardiac chambers, giving an abnormal, mirror image of the heart and aorta, and a normal disposition of abdominal viscera, and a reversed electrocardiogram. (3) Isolated congenital dextrocardia with normal relation of diameters. The heart is located on the right side, the aorta passes across the left bronchus. A normal electrocardiogram is obtained. (4) Acquired dextrocardia possessing the same characteristics as type III but differentiated by the existence of pathologic changes in the neighboring organs. Combined roentgen-ray and cardiographic studies help differentiate the different types. The level of the diaphragm is determined by the location of the heart and not the liver. That half of the diaphragm on which the heart rests occupies the lower level.

C. RHEUMATIC HEART DISEASE

Swift, Derick and *Hitchcock* have discussed bacterial allergy to nonhemolytic streptococci in its relation to rheumatic fever. They have said, "One of the causes of confusion resulting from the reports of the results of different observers has been the variety of streptococci which have been isolated from patients with rheumatic fever. Each worker is naturally inclined to attribute a specific etiologic rôle to the strain isolated by him. The hypothesis that in rheumatic fever there is a hypersensitive state, which is not strictly strain specific, but which embraces a wide range of streptococci, reconciles these divergent observations. It makes understandable the possibility that the microorganisms described by the following workers, to mention only a few, may indeed have been the exciting agents of the active disease in the patients from whom they were recovered: the *streptococcus cardioarthritidis* of Small; the inulin fermenting anhemolytic streptococcus of Birkhaug, the strains described by Clawson, the *micrococcus rheumaticus* of Poynton and Paine, and the three types found by Rosenow. It also explains the possible etiologic rôle of the strains recovered by us in the past fifteen years, despite their great cultural and immunologic variation."

Kaiser has reported the tests on 800 children, 1 week to 16 weeks old, of intradermal injections of 0.1 cc. of a 1-100 dilution of the toxic filtrate from cultures of the non-methemoglobin forming streptococcus isolated by Birkhaug from cases of rheumatic fever. Of the total, 32 per cent. reacted positively. When the entire group was subdivided into three divisions, a definite parallelism was found between rheumatic infections and skin reactions. When there was a history of rheumatic infection, 72 per cent. showed positive skin tests, when there was a history of many sore throats 35 per cent. were positive, and when neither rheumatic infection nor frequent sore throat occurred, only 20 per cent. were positive.

Small has discussed the specificity of the organism which he has isolated in rheumatic fever and which he has named *streptococcus cardioarthritidis*. Rheumatic fever, active rheumatic heart disease, and chorea have been favorably influenced in his hands by the antiserum produced by the organism.

Small has reported further studies of his *streptococcus cardioarthritidis*. He treated 251 patients with antiserum produced by this organism and found benefit in chorea and acute rheumatic fever following its use. Also cardiac and pulmonary involvement was controlled as well as subcutaneous nodules. The twitching in

chorea stopped within a week after the antiserum injection. Protection lasted apparently about 4 to 5 weeks. The antiserum is prepared both from horses and from cows, the bovine antiserum being preferable because, though of equal efficacy, it produces less serum sickness. To prevent relapses, Small advises active immunization with the vaccine after the antiserum has been given.

Kugel and *Epstein* have reported an interesting study of the pulmonary valve, artery and arteriomuscular junction in 24 cases of active rheumatic infection of the heart and in 106 control cases, 31 of which had nonrheumatic pericarditis and 75 neither rheumatic heart disease nor pericarditis. In a large number of the active rheumatic cases there were characteristic lesions not found in the control cases at all. Fourteen of the 24 rheumatic hearts showed interstitial valvulitis of the pulmonary valve and 3 of these 14 showed Aschoff bodies in the valve itself. Verrucae of this valve were conspicuous in 2 cases but present in 4 others also. Active inflammation, with Aschoff bodies in some, was found in the arterio-ventricular junctions of the right ventricle in as many as 17 of the 24 active rheumatic hearts. The pulmonary artery showed active inflammatory changes in intima and media in 5 cases—these were similar to the lesions in the aorta due to rheumatic infection described by Pappenheimer and von Glahn. In 2 cases, these pulmonic artery lesions were macroscopic. In this same series of 24 cases, the aorta, aortic valve and ventriculoaortic junction showed active rheumatic lesions in 22 or 90.7 per cent.

Paul has written on the pleural and pulmonary lesions in rheumatic fever. "We have discussed the pleural and pulmonary lesions which occur in rheumatic fever, which in the past have apparently received more attention from the clinician than from the pathologist. They are probably more common and perhaps of more significance than we have been hitherto led to believe. Among many features they serve to emphasize the rather widespread effects of this disease, of which the cardiac lesions, or in fact the thoracic lesions, are after all, but local manifestations.

"We have remarked upon the fact that pleurisy, generally with effusion, is a relatively common lesion of rheumatic fever, particularly in association with cases of carditis generally indicating a severe rheumatic infection. It is perhaps another example of the selective manner in which this disease manifests itself upon serous surfaces. As a rule it is characterized by the accumulation of fibrinous exudate or of an effusion, which, together with the enlargement of the pericardial sac, often with frank pericarditis, is an injurious combination leading to widespread compression of the lungs. This situation coupled with cardiac embarrassment adds considerably to respiratory distress which is such a frequent symptom of this disease.

"The presence of histological lesions in the walls of the pulmonary arteries and perivascular spaces has been confirmed as a finding encountered in about 20 per cent. of a group of active fatal cases. We have in this process a hitherto unrecognized lesion which may be widespread throughout the lungs.

"Frank bronchopneumonia may occur as an intercurrent infection at any stage of rheumatic fever but it is relatively uncommon. The question as to whether a specific form of rheumatic pneumonia exists has been discussed. Many of the cases which we have had the opportunity of studying at necropsy, particularly those occurring in childhood have presented an acute focal hemorrhagic, lobular pneumonia exhibiting certain atypical features which might serve to differentiate them from the usual type of secondary pneumonia. Sufficient evidence has not accumulated to maintain that this lesion is a specific manifestation of rheumatic fever although it seems to be a fairly characteristic finding."

D. SUBACUTE BACTERIAL ENDOCARDITIS

Weiss and *Rhoades* have reported a study which changes somewhat the usual concept of vegetative endocarditis. They conclude that "the manifestations of subacute bacterial endocarditis may be quite variable. The patient may show a severe septicemia with generalized toxic and embolic manifestations, or may have complete absence of symptoms and signs with pathologic evidence of complete healing. It is probable that the well recognized form of the disease, with toxic and embolic manifestations, represents only one group of patients suffering from the disease. These observations indicate that chronic valvular disease may result from healing or healed bacterial endocarditis, and that the prognosis in this disease may vary greatly with the patient. The diagnosis of mild cases of subacute bacterial endocarditis may be very difficult."

Schlesinger in reporting 14 cases of subacute bacterial endocarditis in children found 6 with previous rheumatism and 2 with congenital cardiac lesions. From the clinical course in children, especially the absence of pericarditis, the infrequency of subacute bacterial endocarditis at this age in spite of the high incidence of rheumatism, he concluded that these diseases could not be considered etiologically the same.

Grant, Wood and *Jones* have attempted to find mechanical cause for the localization of infective processes on heart valves. They reported that "small platelet thrombi occur with greatest frequency on those valves specially liable to subacute bacterial endocarditis. These thrombi are not themselves the result of bacterial invasion but are probably due to local secondary change in the thickened valves. Such "thrombi", the authors add, "can be regarded as offering passing organisms a suitable foothold and nidus for

their establishment," and they further suggest "that if streptococcal invasion of the blood stream occurs at a time when a thrombus is forming on a heart valve then the conditions are suitable for the development of subacute bacterial endocarditis". *Grant, Wood* and *Jones* further carefully examined 86 hearts (22 with "rheumatic" valvular disease, 10 with congenitally bicuspid aortic valves, 14 with syphilitic aortic valve involvement and 40 with normal valves) to determine whether or not valve recesses (pockets and crevices) or valve projections in the form of connective tissue thickenings covered with endothelium could be regarded as offering bacteria a foot-hold for the production of subacute bacterial endocarditis. They found no evidence that such recesses or projections could be responsible in themselves for the bacterial invasion.

E. ANGINA PECTORIS

Keefer and *Resnik* have published a clear analysis of the various theories of the mechanism of angina pectoris with an exposition of the one which seems most satisfactory, namely, that the syndrome results from a relative myocardial anoxemia from such factors as coronary disease, anaemia, and aortic regurgitation.

Stolkind has recorded four new cases of angina pectoris in childhood at the ages of 9, 10, 13 and 14 years—one related to aortic and mitral valve disease, one coming after severe effort (cycling) and two unexplained. *Levin* reports another case in a child.

Moschowitz has described the syndrome "tobacco angina pectoris". The pain is described as more intense and of longer duration than true angina. He related it to previous "tobacco heart" of which two types exist, according to the author "(a) those in which evidence of cardiac injury is not present and (b) those in which the signs are suggestive of the interventricular conduction disturbance associated with coronary or aortic disease." He advised complete withdrawal of tobacco and said that the pains may continue for weeks or months after stopping tobacco. He suggested vasoconstriction spasm as the cause.

F. CORONARY OCCLUSION

Parkinson and *Bedford* have carefully reported the clinical study of 100 cases of cardiac infarction, the autopsy findings of 83, and the electrocardiographic findings in 28. Of the latter, the chief changes occurred in the T wave and R-T segment, only 4 of the latter cases were proved by autopsy.

East, Bain, and *Cary* have described 8 cases of the relatively rare type of cardiac infarction without pain but with sudden, severe dyspnea.

Miller and *Weiss* have reported the discovery at autopsy of normal heart weight in 19 cases of marked coronary disease. In two cases, the enlargement present was due to dilatation.

Boyd has demonstrated acute inflammation of atheromatous plaques as the final cause of coronary thrombosis in 2 cases and believes that an extensive suppurative process in an arteriosclerotic patient may result in an exacerbation of acute arteritis in these areas resulting in a fatal thrombosis.

Kohan and *Bunin* reported a case of coronary occlusion in whom dilatation of the heart to the right and acute hepatic engorgement favored a diagnosis of right coronary blocking which was proved by necropsy.

Allan's study of 1000 consecutive autopsied cases in relation to coronary disease is important. There were 371 cases in which note was made by naked-eye observations of a lesion, whether trifling or severe, of the coronary arteries. Of these 371 cases, 238 showed a definite lesion of the myocardium; 178 present fibrosis, either patchy or diffuse; 12 fibrosis with fatty change, and 48 fatty change alone. In 133, or 35.9 per cent., no obvious change was present, or there was only simple or brown atrophy or hypertrophy. Thus the predominant lesion present was fibrosis, as it was found 190 times (51.2 per cent.) in 371 cases with coronary artery lesions. In the remainder of the 1,000 cases in which no lesion of the coronary arteries was noted, fibrosis occurred in only sixty-eight (10.8 per cent.). The lesions found in these 371 cases, with the percentage incidence of fibrosis, were as follows: atheroma, 299, with fibrosis in 153; arteriosclerosis, 168, with fibrosis in 92; calcification, 40, with fibrosis in 31; syphilis (at or near an orifice), 13, with fibrosis in 5. Using fibrosis, then, as an index of the effect of the various lesions of the coronary arteries, it was found that calcification when present was the factor most likely to produce a lesion of the myocardium. It was usually found in association with atheroma or with atheroma and arteriosclerosis. There were 97 cases in which the lesion of the arteries was specially noted as producing definite narrowing or actual blockage of the lumen. Atheroma was present in 85, with fibrosis in 82 per cent.; arteriosclerosis in 31, with fibrosis in 84 per cent.; calcification in 33, with fibrosis in 85 per cent., and syphilis in 7, with fibrosis in 57 per cent. Fibrosis was present in 78, or 80.5 per cent., of the 97 cases, in contrast with 51.2 per cent. of the whole group. Thus, it may be inferred that when a lesion is sufficiently severe to narrow the lumen, no matter what the lesion, fibrosis is the natural result. Fifty-eight patients died suddenly from coronary artery disease, or disease in which there was definite occlusion of a coronary artery or main branch. Of the 58, atheroma was present in 49; arteriosclerosis in 13; calcification in 20, and syphilis in 11. It is important to note that while this group is a

little less than one-sixth of the total, about one-sixth of the cases of atheroma are found in it, one-half of the cases of calcification, three-fourths of the cases of syphilis, but only one-twelfth of the cases of arteriosclerosis. This supports the view that the atheroma, the commonest lesion, is also a serious one, while calcification or syphilis materially increases the gravity of the case in the direction of promoting occlusion of the vessel. Fibrosis was present in 48 of these cases, but there were 10 in which there is no note of any fibrosis in the heart muscle. From this study, in addition to the general information regarding the frequency of the lesions and their effects, three points emerged which are worthy of note: 1. Severe coronary artery narrowing may be present without obvious lesion in the myocardium. 2. Old standing severe arterial lesions and actual occlusion with fibrosis may be present without a clinical history of their occurrence. 3. Patients may die with symptoms suggesting coronary artery occlusion in whom no such lesion is found.

G. MYOCARDIAL DISEASE AND HYPERTROPHY

Clawson has reported his findings of two anatomical types of myocardial injury noted in many of 429 cases of cardiac failure studied in detail both by gross and by microscopical examination. "First, there are the inflammatory injuries which are shown as exudative or proliferative changes either in localized areas, (as Aschoff nodules or abscesses) or scattered diffusely throughout the heart in the interstitial tissues. The inflammation shows a great tendency to be arranged about blood vessels and upon healing to leave scars with a periarterial arrangement. The second type of myocardial injury is the myocardial fibrosis without any evidence of an association with inflammation. These scars appear as areas of atrophy of the muscle fibers with a replacement by connective tissue. This second form of myocardial scar is a definite result of coronary sclerosis of the senile type.

"The inflammatory type of myocardial injury is common in all forms of rheumatic and bacterial valvular injuries, but it is rare in the myocardium in syphilitic aortitis. It occurs seldom or not at all in the myocardium in cases where death results from essential hypertension or from coronary sclerosis. The atrophic scars are rarely found in cases of cardiac failure except in the groups having hypertension and coronary sclerosis. Myocardial fibrosis of either the inflammatory or the atrophic type is seldom present to a severe extent except in the group where death results from coronary sclerosis. Here it is found in only a relatively small percentage of cases.

"The result of the active myocarditis probably is somewhat of a factor in bringing about cardiac failure, but the atrophic form of fibrosis, even in its severe degree, does not seem to be of much importance as a cause of death.

"It is doubtful whether the clinical diagnosis of either acute or chronic myocarditis should be made, even though such a condition commonly exists in association with a valvulitis. It is certain that what is called chronic myocarditis clinically in chronic heart failure without valvular injury is not an inflammatory condition and in most cases there is not any other condition in the myocardium showing an anatomical basis for the failure. So-called myocarditis is usually a condition of the myocardium, probably fatigue, which is not manifested anatomically."

Christian has written interestingly of chronic non-valvular disease of the heart, consisting of enlargement or failure, or both, without disease of pericardium or valves. He believes that the term "chronic myocarditis" should now be given up in describing this condition since in the majority of hearts at post mortem examination, the muscle "looks very healthy and normal, both macroscopically and microscopically." Sometimes fibrosis due to coronary disease is found and sometimes "small foci of infiltration with lymphocytes and plasma cells, usually perivascular in distribution". The chief finding, however, is cardiac hypertrophy and eventually fatigue and failure. Christian has replaced the term "chronic myocarditis" which he formerly used by "chronic myocardial insufficiency" which he finds also rather unsatisfactory in describing this condition. He emphasizes the value of digitalis in the treatment of this type of heart failure.

H. HYPERTENSION

O'Hare, Calhoun, and *Altnow* have contributed to an understanding of the cases of heart disease commonly called "chronic myocarditis". They studied 50 cases without valve disease or hypertension at the time of examination. All had some cardiac weakness. With one exception, all showed retinal arteriosclerosis and, on careful review, all were found to have had systolic blood pressures in the past varying from 160 to 235 mm. mercury. In a control group of 38 with valvular disease and myocardial insufficiency, retinal sclerosis was found in only 8, several of whom were known or thought to have had previous hypertension.

The pathological study by *Bell* and *Clawson* of 420 cases of primary hypertension is a valuable survey. The renal arteries within the parenchyma of the kidney showed sclerosis (hyperplastic-elastic intimal thickening) of varying degree in 97.6 per cent. of the cases, but only 8.5 per cent. died of uremia.

Keith, Wagner and *Kernohan* stressed the characteristic histologic picture in "malignant hypertension" of diffuse general hypertrophy of arterioles. The terminal picture is one of simultaneous, rapid, functional failure of brain,

heart, and kidneys. It is to be distinguished from benign hypertension and chronic glomerulonephritis. The chief points of distinction from the latter are the age incidence, the characteristic renal picture and the frequent adequacy of renal excretion.

Cutler's pathological work on 18 cases of hypertension seems to disprove the theory put forward by Barker and Bordley that hypertension is a functional response to lessened circulation in the pons and medulla due to arteriosclerosis of blood vessels in this region, at least so far as demonstrable anatomic change is concerned.

Levine and *Fulton* found an increased incidence of hypertension in cases of mitral stenosis over the age of 45, beyond the normal occurrence of hypertension at this age. This was based on a study of 762 cases of mitral stenosis. They attribute this to a double vulnerability of these patients to infections and degenerative cardiovascular disease.

Dumas has confirmed this finding.

I. MISCELLANEOUS

(a). *Neoplasm. Bradley* and *Maxwell* have published a report of the first case of primary rhabdomyosarcoma of the heart. The patient was a man of 62 with symptoms of pain in the left upper part of the chest for several weeks and marked edema of the neck and face for several days. X-ray films showed a "mediastinal tumor and smaller tumor masses in the right lung." The heart dulness was considerably increased. At post mortem examination a soft friable tumor was found filling the pericardial cavity and almost completely surrounding the heart. "The epicardium was almost completely destroyed. The tumor tissue invaded the heart muscle but at no place did it extend very deeply. A number of metastatic nodules measuring from 2 to 10 mm. in diameter were found in the myocardium of the septum and left ventricle. Both lungs showed numerous metastatic nodules. The liver and both kidneys presented a few small tumors." Microscopic examination showed rhabdomyosarcoma. A review of the literature showed 38 cases of primary sarcoma previously reported.

(b). *Pregnancy — Hamilton* and *Kellogg* have summarized their experience at the Boston Lying-In Hospital. They divided these cases into three groups: class 1—with definite heart disease (252 patients with 21 maternal deaths), class 2—with "possible" heart disease (276 patients with 2 maternal deaths, not from heart disease), and class 3—without heart disease, but in the main, neurocirculatory asthenia (149 patients with no deaths). Class 1 they subdivided into 1A and 1B—those in 1A including the more serious cases not tolerating pregnancy well, namely, those with heart failure, past or present, auricular fibrillation, or hypertension. Patients of class 1A, the authors believe, should be warned against pregnancy, aborted therapeutically if seen early in pregnancy, and sterilized when practicable. Class 1B patients should be watched very closely to avoid failure and death. The type of anesthesia and obstetric procedure on delivery are less important than prenatal advice and care.

Walser has reported two cases of subacute bacterial endocarditis in pregnant women. Delivery did not affect the condition at all. One infant, premature, lived 17 hours and died from streptococcus viridans infection as shown by culture. The other infant survived at full term, but at first showed a similar bacteriemia.

(c). *Nutritional Diseases.* (Beri-beri) *Aalsmeer* and *Wenckebach* have described the effect of vitamine B deficiency on the heart.

Mebius reported three cases with changes in the right heart.

Scott and *Herrmann* in their study of the disease in Louisiana, report that "Death in the acute cases is probably due to bilateral vagus degeneration and possibly to failure of the right ventricle and general myocardial injury". At autopsy in one case, a large, dilated heart was found. The electrocardiogram was suggestive of myocardial changes.

(Rickets). *Meixner* found left ventricular dilatation at necropsy in eleven children with rickets who died suddenly.

(d). *Aneurysm. Dandy* reported 8 cases of arteriovenous aneurysm of the brain. Twenty-two have been previously described. They may be located in any part of the brain and usually cause Jacksonian attacks for many years. They account for about one per cent. of brain tumors.

(e). *Cysticercus. Pulgram* has reported the unusual case of a man 26 years old with attacks of headache, dizziness, tinnitus, vomiting and syncope who died suddenly, and whose post mortem examination showed numerous cysticerci in brain, dura, myocardium and skeletal muscles. One cysticercus lay in the region of the auriculo-ventricular bundle (of His).

(f). *Mushroom-Poisoning. Hyman* has described a case of poisoning by the mushroom *Amanita phalloides.* Electrocardiogram showed right bundle branch block and ventricular premature beats which were thought to be the probable result of myocardial damage from the poisoning, especially since the bundle branch block had almost entirely disappeared nine months later.

(g). *Air embolism. Rukstinat* and *Le Count* report their observations on 22 guinea pigs into whose trachea air was forced under a pressure of 20 to 80 mm. of mercury. "With 45 mm. of pressure or more, the pigs always died in from fifty to seventy-five seconds. After death the bodies were examined under water at once. In all the guinea pigs the lung parenchyma was diffusely speckled with petechial hemorrhages. In all the animals there was some pneumothorax, with air in the aorta, carotid, brachial and iliac arteries and frothy blood in all the heart

chambers. There was always air in the coronary arteries. In three-fourths of the animals it resembled silver filigree beneath the epicardium, the air filling from 50 to 90 per cent. of the channels and being interrupted here and there with blood."

(h). *Pulmonary Thrombosis. Ljungdahl* reports the cases of two women, who suffered for years with dry cough. Dyspnea developed and grew continually worse, then came cyanosis, palpitation of the heart and finally symptoms of cardiac insufficiency, edema, ascites, etc., with fatal termination. In each case necropsy showed obstruction of the pulmonary artery by thrombus, dilatation of the central section of the pulmonary artery, as well as marked dilatation and hypertrophy of the right side of the heart, while the valvular apparatus was entirely intact. Lungs and bronchi appeared normal. The author thinks that in all probability a stenosis of the pulmonary artery was present during life, but whether the stenosis was caused by a thrombus cannot be ascertained. He finds it difficult to explain the cough in the absence of pulmonary or bronchial changes. A similar cough was observed in a case of long-continued mitral stenosis.

(i). *Athletics. Eimer,* in an article in the *Deutsche medizinische Wochenschrift,* discusses some of the most recent researches in this field, which bring out some remarkable and noteworthy observations. His point of departure is the fully established fact that, after a single bodily endeavor, the heart, as a rule, is not distended, as might be expected, but contracted. It is remarkable that the heart adapts itself to suddenly increased demands on it by diminution of the output, while the number of pulse beats is increased at the same time. The diminution of the output persists for some time after the performance, even though the pulse beat and the blood pressure have become normal. The contraction of the heart associated with a single bodily performance is only transient, and only in exceedingly rare cases does it have any permanent effects. But what is the effect on the heart of an excess bodily task continued over a period of years? Those animals which execute great muscular performances, for example the deer, the race horse and swiftly flying birds, have especially large hearts. In the hare, for example, the heart is almost three times as heavy as in the caged rabbit. This principle that, the greater the tasks performed, the larger the heart is, appears to apply to man as well. The marked effect of military service on the size of the heart has been noted. Eimer examined the hearts of the contestants in the Olympic games held in 1924 in Marburg and compared them with the hearts of normal Marburg students. He found that the healthy hearts of students aged 18 to 23, even after several months' training and following remarkable bodily performances, showed no essential change in size. On the other hand, in the hearts of the older students, the effects of many years' participation in sport activities could be discerned in the form of a broadening of the heart transversely. As the result of long-continued, repeated excess demands on the heart, a moderate enlargement of the heart shadow can be expected, but it is not yet established whether this enlargement injures the heart.

III. Symptoms and Signs

A. SYMPTOMS

Swift and *Hitchcock* have studied the relationship of precordial pain to active rheumatic infection of the heart. They concluded that "a higher percentage of patients with precordial pain during the acute infection had permanent valvular injury than those who were free from pain.

While freedom from cardiac pain did not insure freedom from cardiac involvement, the great frequency with which the two were encountered together indicates that cardiac pain manifested by a patient with rheumatic fever should be regarded by the physician as a special indication for treatment calculated to safeguard the heart."

Wassermann believes that the mechanism of cardiac asthma and acute pulmonary oedema is not that primarily of acute left ventricular failure such as is generally held, but that it is a reflex disturbance due to sympathetic stimulation of bulbar nerve centers coming from the heart and aorta and giving rise to tachycardia, increased blood pressure and dyspnoea, probably with pulmonary vasoconstriction. Following this sequence of events, there appear the asthmatic breathing, and, if the attack is severe, well marked oedema. Nitrites, morphine, but especially vagal pressure, Wassermann recommends for the control of this cardio-aortic-bulbar-pulmonary reflex phenomenon. Like angina pectoris, the condition is usually found with left ventricular or aortic disease but not with heart failure, he believes.

Brunn explains the mechanism on the basis of an obstruction in the pulmonary capillaries due to disturbance of renal function interfering with the excretion of urine during the attack. This explains the increase in urine after the attack and the relief by pituitrin which acts to retain fluid in the tissues.

Pal has studied the action of gastric pneumatosis, hypotonia of cardia and angina pectoris. Pneumatosis from sucking air is usually harmless. Pneumatosis from swallowing air with poorly masticated, hastily swallowed foods may cause serious symptoms, especially in elderly persons. It is made worse by ingestion of beverages containing carbon dioxide and by taking sodium bicarbonate. Frequently the stomach still further increases its content of air by aspiration, if the cardiac sphincter is hypotonic. When a large amount of air enters the

stomach, it rises into the fundus; the distended fundus raises the left part of the diaphragm and closes the cardia. This variety of closure of the cardia is often mistaken for cardiospasm. This process is much more frequent in men than in women, since in women the stomach usually lies lower. In young persons, also, the stomach can contain a large amount of air without producing symptoms. The degree of fulness of the intestine, particularly of the transverse colon and the left flexure, has an influence on the effects of gastric distention; a full intestine raises and compresses the stomach. Extrasystoles may be caused by reflex action. Dyspeptic asthma is usually a result of pneumatosis with hypotonia of the cardia. There is a form of gastric distention that depends wholly on emotional excitement. In these cases there is usually a hypotonic cardia, but it appears that the permeability of the cardia may occur acutely. If the stomach is greatly distended with air, the cardia may be closed entirely; the oesophagus may then become so distended that its mechanical action on the heart causes the latter to stop. Death may result, though the usual course is prompt recovery. Pneumatosis of the stomach may simulate angina pectoris, it may be an inciting factor, or it may accompany it.

B. SIGNS INCLUDING SOUNDS AND MURMURS

Palmer and *White* have reviewed the cases of fourteen children who showed a continuous humming vascular murmur best heard on the right side of the neck, also heard in the infraclavicular fossa, over the manubrium sterni and sometimes on the left side of the neck. They call attention to the importance of recognizing this common normal physical sign in childhood, which however, is not usually done. In their series of fourteen cases, patent ductus arteriosus had been wrongly considered three times and aortic regurgitation twice.

White has studied 100 patients showing gallop rhythm and found the sign related to coronary disease in 54% with coronary thrombosis in 21%. Hypertension was present in 49%; syphilitic aortitis in 13%; rheumatic heart disease in 12%; nephritis 12%; uremia 10%; effort syndrome alone in 3%; pericarditis in 3%; subacute bacterial endocarditis in 2%; congenital heart disease 1%; and unknown factors 5%. In organic heart disease especially with hypertension or coronary disease it is usually a sign of grave importance. Almost half of the 100 cases died in one year after the discovery of the sign.

Mudd and *White* have emphasized the clinical importance of the auscultatory gap in sphygmomanometry because of the error that may be occasioned if the possibility of its occurrence is disregarded. Thirty cases are reported and analyzed. Hypertension was evident in twenty-eight patients (93 per cent.) and aortic stenosis in four (13 per cent.). Each case showed hypertension or aortic stenosis, or both (two cases). No definite prognostic significance is attached to the auscultatory gap, the outlook depending on the underlying pathologic condition in each case.

Kauf and *Zak* have reported a study of the secretion of sweat in cardiovascular disease. They call attention to the simultaneous increase of output of urine and of sweat that may occur in oedematous patients under diuretic therapy, and they discuss two methods for the observation of the activity of the sweat glands of the finger tips, especially of the fourth finger. These two methods are, first, the microscopic inspection of the droplets themselves, and second, the registration of the sweat secretion of the fingers by pressing their tips for two seconds on a piece of filter paper impregnated with 1% silver nitrate solution, whereby the salt in the sweat precipitates the silver chloride which darkens on exposure to light. Many hypertensive cases investigated showed a decreased sweat secretion, but the clearest findings were in a group of 48 cases of heart disease. Fifteen of these were patients with valvular disease without congestive failure and all showed normal secretion. The twenty-seven cases with outspoken congestive failure all showed absence or clear diminution of the sweat secretion.

IV. X-Ray

A note on the advances of x-ray in cardiology should include mention of the new (4th) edition of *Assmann's* book containing much authoritative material on the subject. The revised work of *Vaquez* and *Bordet* should also be referred to.

Laurell's work on cinematographic roentgenography of the heart has helped this difficult field. Various techniques have been described in recent years both in America and abroad.

Lincoln and *Spillman* have presented an interesting study of 246 normal school children whose heart size has been annually measured by x-ray for 7 years. "There is a closer correlation between height and the size of the heart than between age and the size of the heart. Approximately one third of the heart lies to the right of the midline in children from 4 through 13 years of age. The transverse diameter of the heart is approximately one half of the width of the chest in children from 2 through 13 years of age, and there is no change in this relation with increasing age or height. The drop heart is extremely rare in children from 2 through 13 years of age, occurring in only one of our cases. Accentuation of the pulmonary artery even when marked, has not had any pathologic significance in the cases studied. Serial roentgenograms of the same child usually show great uniformity in contour of the shadow of the heart. There is a strong, familial resemblance in the shadow of the heart in one half of our family groups."

Levy and *Golden* report their study of the therapeutic effect of roentgen irradiation of the heart in 30 patients with rheumatic heart disease. Two hundred and forty-nine irradiations were given to these cases with the machine setting calculated to yield about 10 per cent. of the erythema dose distributed throughout the heart muscle. Changes in the form of the electrocardiogram were observed in 17 of the 30 cases following irradiation. "Of the 30 cases, 21 (70 per cent.) showed clinical improvement at the end of the follow-up period. Three improved temporarily, 1 was unimproved, and 5 died. In 4 cases of subacute bacterial endocarditis due to the non-hemolytic streptococcus, roentgen irradiation of the heart caused no change in the form of the electrocardiogram, nor did it arrest the fatal progress of the disease. It is suggested that in rheumatic fever, roentgen irradiation of the heart may serve to desensitize the tissues of the heart to an allergizing substance, thereby favoring the subsidence of existing lesions and preventing further cardiac damage."

V. Cardiography and Electrocardiography

Matthews has published a description of his new moving iron oscillograph with amplifier. He writes, "The oscillograph is capable of giving more accurate records of nerve action potentials than have been obtained with any other instrument except the cathode ray oscillograph, and it has the advantage over this that it can give a record of a single impulse in one nerve fiber. The instrument is electrically unbreakable. The possible sources of error are discussed, and it is shown by calibration curves that the distortions are very small. The photographic records of this oscillograph suffer from errors of less than 3 per cent. and are in linear co-ördinates."

Thus the author believes the apparatus is superior, for recording nerve (and muscle) action potentials, to the capillary electrometer, string galvanometer, the moving loop oscillograph (of Rosenberg, similar to the Duddel oscillograph), and the cathode ray oscillograph (used by Gasser and Erlanger). This new oscillograph has been introduced also for electrocardiography as well as for recording nerve action.

Fossier has published a study of mechanically elicited ventricular extrasystoles of the heart of a man 39 years old with a congenital malformation of the sternum which totally deprived the heart of bony protection. Six points were selected for stimulation, four in a vertical line from above downwards, 3 centimeters apart, the uppermost being at the base close to the pulmonary artery and the lowest at the apex of the right ventricle. The 5th and 6th points were at the extreme right and left borders of the heart on a level with point 3 and so fell on the lateral and apical portions of the right and left ventricles respectively. Point 1 gave the so-called typical right ventricular extrasystole, points 4 and 6 the so-called typical right ventricular extrasystole, points 3 and 5 less well marked left ventricular deflections, and point 2 transitional forms. Fossier believes that the term "right and left ventricular extrasystoles" should therefore be replaced by the term "basal and apical extrasystoles".

Studies of ventricular tachycardia with special reference to bidirectional complexes have been made by *Palmer* and *White, Smith* and *Marvin*. Its relationship to coronary disease and digitalis has been noted.

Geraudel and *Mouquin* have recommended intravenous quinine hydrochloride to stop attacks of paroxysmal tachycardia.

Scherf has reported experiments on the dog's auricle which, he believes, controvert Lewis's theory that the circus movement in auricular flutter travels around the great veins in the direction of the taenia terminalis. In 16 out of 17 experimental instances, broad cross ligatures of the auricular muscle at the middle of the taenia terminalis failed to stop auricular flutter. In other instances in which the application of ligatures caused pronounced changes in shape of the normal rhythm P waves of the electrocardiogram, similar changes in shape of the flutter waves were produced by the same ligaturing, indicating, Scherf believes, that the auricular flutter pacemaker is in or near the sino-auricular node.

Sprague and *White* have reported a case of auricular flutter which ceased spontaneously after five years—the longest paroxysm with recovery on record.

Schwartz and *Weiss* have reported their observation of the development of auricular fibrillation in 10 out of 60 children with rheumatic heart disease followed for five years. Acute rheumatic fever, mitral stenosis and excessive digitalis were apparently the factors responsible for this very grave finding in children. Four of the cases died within one week, and three more within one year of the appearance of the auricular fibrillation. Five of the ten cases were girls and five were boys.

Palmer and *White* have reported a study of 107 cases showing aberrant ventricular responses to auricular premature beats out of a total series of 387 consecutive cases with electrocardiograms of auricular premature beats. Aberration and the degree of aberration (intraventricular block) in the ventricular response to an auricular premature beat were found to depend mainly upon the degree of prematurity and not upon the state of health of the heart. There seemed to be no relation to prognosis. Also aberration in the ventricular complexes during the height of a paroxysm of auricular tachycardia appeared not to be serious, judging from a review of 4 such cases found among a total of 73 patients with auricular paroxysmal tachycardia. One of these 4 patients was working and in good health 13 years after this finding.

King has reported his study of the clinical recognition of bundle branch block in 100 unselected cardiac patients. Visible and palpable bifid apex thrust and reduplication of heart sounds, especially the first, or a systolic murmur separated from the first sound along with weakness of the sounds were found more frequently in the presence of bundle branch block (8 cases) than in its absence (4 cases). One case of bundle branch block failed to show these signs.

McMillan and *Cook* have confirmed the finding of electrocardiographic changes during rheumatic fever by recording abnormalities in 36 out of 43 cases. Extrasystoles, auriculo-ventricular rhythm, auriculo-ventricular dissociation, auricular paroxysmal tachycardia, various grades of auriculo-ventricular block and changes in the shape of the Q R S and T waves and in the R-T and S-T intervals were all encountered. In addition to these previously reported changes, notching of the P waves was found present in slightly more than 50% of their series. These changes were transient.

Reid and *Kenway* have also studied 26 patients with acute rheumatic fever with 281 electrocardiograms. They found (1) increase in auriculo-ventricular conduction time, (2) alteration in the ventricular complex, and (3) changes in cardiac rhythm.

VI. Other Methods

Interest in percussion has been renewed by a paper by Muller, translated by *Buck*. Some of his conclusions are that "Many physicians believe that the art of percussion and auscultation is out of date, or that it is supplanted by the x-ray and the tuberculin test; but it is just as indispensable today as it was a hundred years ago. It is not only not supplanted by the x-ray, but the art of percussion and auscultation is much more necessary in order correctly to interpret the x-ray picture. Above all, it has gained certainty since being controlled by the x-ray. The chest wall, as well as the vertebral column, vibrate upon percussion not so much in the direction of the thrust as, rather, according to their flexibility. I have never been able to percuss the cardiac dulness in the back, and an aortic aneurysm only when it extended along the spine in the paravertebral space. We shall always find the relative cardiac dulness just at that point where the overlying bit of lung is no thicker than 3 to 5 cm. On this account we shall in general percuss the heart too small when the covering layer of lung is of greater thickness, and this is indeed frequently the case, namely over the right auricle and the great vessels. The central shadows (vena cava, aorta and pulmonary artery) do not cause dulness under normal conditions, and they only betray themselves if they lie unusually close to the chest wall. Otherwise percussion over the sternum gives highly uncertain results because this broad, long bone lies partly over air containing and partly over solid organs and acts like a huge pleximeter. It vibrates more or less as a whole, whether it is percussed above or below, on the right side or on the left. I feel quite certain that the border of relative dulness is the same with either heavy or light percussion. The teaching that we should percuss the relative cardiac dulness with vigorous blows because only such blows will penetrate to the heart and set it into vibration is obviously incorrect. Forcible percussion over the precordia is not desirable because so frequently the impulse is transmitted to the stomach and sets it into vibration with a tympanitic note. We must conclude that an infiltration, a tumor or an aneurysm which is covered by a portion of lung more than 5 cm. in thickness cannot be demonstrated by percussion whether it be gentle or vigorous. The terms resonant and dull, or loud and faint, are of course always relative. The principal task in the course in percussion is to encourage the beginner in an honest method of investigation, and to guard him against the intrusion of previously formed judgments. Hard, bony fingers are better adopted to the purpose (of percussion) than soft, fleshy ones, because the latter have the same disadvantages as the above mentioned thick rubber hammer and the rubber eraser plexi-meter."

Kurtz and *White* have further emphasized the value of percussion with a study of one hundred cases with normal and abnormal hearts by percussion and roentgen ray measurements of the borders of the heart and great vessels. "Percussion is of value for the following reasons: (a) it is reasonably accurate as shown by comparison with the 7-foot roentgen ray plate; (b) a roentgen ray plate is often difficult or impossible to obtain; (c) percussion is simple, rapid and requires no apparatus; (d) it is a valuable check on the accuracy of roentgen ray technique and interpretation.

"The apex impulse is not always as accurate as the left border of dulness, but it is often easier to determine on physical examination. It should always be checked against the left border of dulness in the fifth (or sixth) space and compared with the midclavicular line. Palpation of the apex impulse may sometimes give a more accurate evidence of the position of the cardiac apex than can be obtained from the 7-foot roentgen ray film when the shadow of the apex is obscured by other shadows.

"The nipple line is too variable to be of any value in determining enlargement. The midclavicular line is a much more reliable index.

"Percussion should always be attempted in the third left interspace, as this may be the only portion of the heart which is enlarged to physical examination, as in mitral stenosis and congenital heart disease.

"Percussion in the second interspace, both

to left and to right and in the fourth right interspace should always be attempted, because in case of marked increase, widening can usually be detected even though the measurements themselves are bound to be inexact."

Reference should again be made to the work of *Blumgart* on the development of a method for measuring pulmonary circulation time. His studies have been very important.

Benedict and *Parmenter* have decided that for practical purposes, it is considered that the average person expends the same amount of energy in walking up one flight of steps (fifteen steps, each 20 cm. high) as he does in walking on a level fifteen times the distance represented by the vertical height of such a staircase, or as he does in descending three such flights of steps. These comparisons may be helpful to the physician in prescribing exercise for patients.

VII. Pharmacology

Wilson, Pilcher and *Harrison* have reported experiments on normal dogs showing that ephedrine given intravenously usually causes an immediate increase in the minute cardiac output lasting 15 or more minutes.

"If the drug is given subcutaneously the action is more uniform and of greater degree, developing within fifteen minutes and lasting forty-five minutes or longer. If it is given orally an increase develops after thirty minutes and lasts about an hour." The writers conclude that "ephedrine increases the minute cardiac output, and the results of its use in shock indicate that it is of value as a cardiac stimulant."

La Barre found that ephedrine (which salt La Barre used was not stated), administered intravenously to cats anesthetized with chloroform, does not produce the cardiovascular accidents that are produced by the administration of solution of epinephrine hydrochloride. This fact represents a new difference in the physiologic action of these two substances, which are so closely related chemically. Owing to the absence of an ephedrinochloroform syncope in the cat, the author believes that the pharmacologic point of attack of ephedrine differs from that of epinephrine. Ephedrine, therefore, should not be considered as a purely sympathicotropic substance.

Cohn and *Stewart* have studied the effect of therapeutic doses of digitalis intravenously and by mouth upon the circulation of normal dogs. They found constant changes in the T waves of the electrocardiogram, a slowing of the heart rate, a decrease in cardiac area (as studied by x-ray), an increase of ventricular excursions, a constant initial decrease of cardiac output, at times increasing later, and a return to normal of cardiac size and ventricular excursions after the effect of digitalis wore off. The effects were maximal 2 to 24 hours after the administration of digitalis. These writers conclude that two opposing factors control the cardiac output. The first increases cardiac tone, resulting in decrease in size of the heart and decrease in output. The second factor increases ventricular contraction and tends to increase cardiac output.

Cohn and *Stewart* have in addition studied the effect of digitalis upon the cardiac output, cardiac size and ventricular contraction of dogs with enlarged hearts but without evidence of heart failure. They found that the size of the heart decreased and the extent of ventricular contractions increased, as in normal dogs. "The cardiac output which results is the net result of the effect of digitalis on the two underlying actions. Early, the effect on cardiac size predominates so that the cardiac output diminishes. Later the effect on ventricular contraction may predominate, so that cardiac output reaches its original normal volume or even overshoots it, at a time when the size of the heart is still relatively small." The authors add a word of warning that enlargement of the heart from mechanical embarrassment may require differentiation from the enlargement due to underlying disease (in which oedema is conspicuous).

Smith, Burwell and *DeVito* have reported their study of the effect of 1.2 mgm. of atropine sulphate administered intravenously to six normal men. There resulted a marked rise in heart rate, a relatively small rise in cardiac output per minute and no change in pulse pressure or metabolic rate. The acceleration of the heart rate was accompanied by a diminution of the output of the heart per beat.

Camp has concluded, after experiments on frogs, white rats and rabbits, that "cardiazol has no apparent effect on the normal heart. It effects convulsions by acting on the medulla. It produces its change by acting on the autonomic centers in the brain" creating a mixed sympathetic and parasympathetic picture. From the experimental view point its clinical application is questionable.

Barker and *Levine* have reported experiments which show that in both normal cats and in those depressed by quinidine, hemorrhage, and acid intoxication, metrazol has no beneficial effect on the cardiorespiratory mechanism.

Melville and *Stehle* found that mercuric chloride dissolved in serum has an extremely marked diuretic action when injected intravenously. When injected into one of the renal arteries, mercuric chloride produces only diminution of urine secretion. This result, together with the conclusions which may be drawn from the composition of the urine secreted, indicate that the diuresis is due to an extrarenal action. The diuresis is not accompanied by any increase in lymph flow from the thoracic duct. Except for the latent period before diuresis begins, the action of mercuric chloride is identical with that of merbaphen.

VIII. Treatment

A. Medical

Quinidine

Spiro and *Newman* have reported a new series of cases of auricular fibrillation treated by quinidine sulphate with a high percentage of temporary success in the restoration of normal rhythm. Of 41 cases, 35 were restored to normal rhythm (80 per cent.) and 21 of these continued to show normal rhythm for a year or more. The quinidine was given 4 grains the first day, 8 grains the second day, and then 8 additional grains every 24 hours for 10 days, or until the patient was taking 72 grains in 24 hours. The drug was given at intervals day and night. If the first course was unsuccessful a second course with larger doses was given after an interval of a few days. Digitalis was used before and for the first three days of the course of quinidine. The authors believe that "in auricular fibrillation, when one sees fluoroscopically the ventricles contracting and expanding with vigor, one has a fairly safe index for quinidine therapy" with little danger of a loose intracardiac thrombus.

Bramwell and *Ellis* report definite benefit of long duration from the use of quinidine sulphate in one-third (9) of a series of twenty-seven unselected hospital cases of auricular fibrillation. In ten other cases normal rhythm was restored, but it was of such short duration, or the condition of the patient was so little benefitted by its restoration that the results of the therapy could not be considered successful. In eight cases the auricular fibrillation was not abolished at all by the quinidine. Twenty-two of the twenty-seven cases seemed to be rheumatic in nature.

Herrmann has reported satisfactory results from the use of quinidine sulphate therapy in auricular fibrillation, 65% of 18 cases having been restored to normal rhythm. Etiology and duration of the arrhythmia he found to be unimportant factors. With a rapid ventricular rate he recommends preliminary digitalization. Heart block, marked congestive failure and serious myocardial disease he considers contraindications to the use of the drug.

Levine and *Stevens* report a case of coronary thrombosis in which a persistent ventricular tachycardia developed with a heart rate of 200. This lasted for several days, and the clinical condition seemed desperate. Quinidine sulphate in extremely large doses proved successful in restoring the heart to a normal rhythm. It was only after 1.5 gm. was given five times a day that the normal rhythm was maintained. Considerable aid was obtained from taking frequent electrocardiograms, for when the dose of 1.2 gm. of quinidine sulphate had been reached, the heart tracing showed that a partial effect had been already obtained.

Bourne reports the restoration to normal rhythm of a chronic rheumatic heart with established auricular flutter in a young subject, by massive dosage of quinidine sulphate (750 grains).

Haskell has reported the results of experiments on dogs in which injections of a 1% solution of quinidine sulphate quickly abolished the gross disturbances of heart rhythm induced by toxic amounts of digitalis. "The indications are, apparently, that the ability of quinidine to restore regular cardiac action when this has been disturbed by toxic doses of digitalis is due partly to the action on the vagal endings; and, to a less extent, to a direct influence on the myocardium."

Digitalis

Pardee has further studied preparations of digitalis for intravenous use. For patients who have not had digitalis, he recommends 1 minim per pound of body weight (½ the therapeutic dose) of digalen, digifolin solution, or digitan hypodermic; and 1/100 gr. digitalin (amorphous) Burroughs and Welcome Co. per 18 pounds of body weight. In auricular fibrillation, slowing occurs in five minutes after injection and becomes marked in thirty minutes. T wave changes appear in 2-4 hours.

Rothman and *Leonard* report on the effect of digitalis in two cases of heart failure in infants. The histories of both children were almost identical. One was 14 months of age and the other 16 months. There was no evidence pointing to either a rheumatic or diptheritic etiology. Their illnesses were of short duration, and on admission they were suffering from myocardial decompensation. Their hearts were tremendously enlarged, and the roentgenograms were similar to those in cases of idiopathic hypertrophy of the heart. Digitalis was administered, and was followed by prompt improvement. Although the etiology of the myocardial failure is still a matter for speculation, the response to digitalis was sufficiently conclusive to warrant the use of the drug in similar cases.

Ephedrine

Stecher has reported a case, a man 65 years old, with complete heart block and syncope with convulsions due to ventricular standstill, completely relieved by the administration of 20 to 30 milligrams of ephedrine three times a day during three weeks of administration and for ten weeks afterwards. Before the administration of ephedrine was begun, 10 minims of epinephrine subcutaneously had afforded almost instant relief lasting several hours at the time of the acute Adams-Stokes attacks. Barium chloride 30 miligrams three times a day helped for a few days but then failed and was successfully replaced by the ephedrine.

Bloedorn and *Dickens* in a case reported, observed signs of serious cardiac embarrassment, including pulsus alternans, marked tachycardia and cardiac decompensation, after the use of ephedrine for a condition diagnosed as "asthma". The authors warn that ephedrine is a dangerous drug to use when patients show evidence of cardiac injury. Extreme care is neces-

sary in the diagnosis of bronchial asthma, as not infrequently cases of so-called cardiac asthma are put in this group. Ephedrine may produce acute cardiac decompensation and pulsus alternans in patients with injured hearts. If during the administration of ephedrine the patient exhibits any toxic symptoms such as palpitation, tachycardia, arrhythmia or vasomotor disturbances, the drug should be promptly discontinued. Pulsus alternans does not have the serious significance for patients who exhibit this condition with tachycardia that it has for persons with a normal cadiac rate. The sale of ephedrine to the layman should be discouraged, and its indiscriminate use by the physician is to be deplored.

Salyrgan

Barker and *O'Hare* have studied during the past year the effect of salyrgan in a series of thirty patients with edema complicating the following conditions: cardiorenal disease 19 cases, nephrosis 3 cases, malignant disease with ascites 3 cases, cirrhosis of the liver 2 cases, tuberculous peritonitis 1 case, pleurisy with effusion 1 case, and malignant disease with chylous pleural effusion 1 case. From the study they have concluded as follows:

"(1). Salyrgan is a good diuretic with a wide range of usage, and it is relatively non-irritating.

"(2). It is of particular value in circulatory failure and the ascites due to cirrhosis of the liver and chronic nephrosis. It may be of help in the ascites of malignant and inflammatory origin.

"(3). Salyrgan, like merbaphen, is much more effective in the presence of acid-forming salts, and the ammonium ion seems to be most effective when supplied as ammonium chloride or nitrate" (in the dose of 8 to 15 grams daily, started 3 to 4 days before the administration of the salyrgan.)

Urea

Simici, Marcou and *Popescu* have written of the diuretic action of urea and believe it to be the most vigorous and constant of diuretic drugs in the treatment of transudates and exudates. They recommend daily doses of 25 to 50 grams for 3 to 7 days followed by several days of rest. They have found that the amount of diuresis is proportional to the amount of urea given. The diuresis may continue for 24 hours after the drug is stopped.

Parathyroid

Reitzel and *Stone* have reported an interesting case of rheumatic heart disease, mitral stenosis, congestive failure, auricular fibrillation and pregnancy (a woman of 28 years) in whom a persistent oedema failed to clear up under the administration of rest, digitalis, theophylline-ethylenediamine, ammonium chloride, and theophylline, but did yield entirely to 50 units of parathyroid extract—Collip given subcutaneously. The authors conclude that "The response to the parathyroid extract seems to indicate that in certain instances the removal of the oedema is not to be found in improved heart or kidney action but in some osmotic change in the edematous tissues themselves."

Salicylates

Derick, Hitchcock and *Swift* have shown that "if, immediately following the discontinuance of serum therapy, neocinchophen or aspirin in adequate dosage is given to patients and continued throughout the usual period of serum disease, arthritis is usually prevented even though other manifestations of serum disease occur. The serum of patients treated in this manner usually fails to contain anti-horse serum precipitin, and only rarely shows a precipitin concentration above 1:40. Usually a precipitin content of 1:400 is necessary before the patient shows arthritis. The theory is advanced that urticaria in serum disease is the result of active sensitization of the skin which is not prevented by the drug treatment, while the arthritis is the result of passive sensitization of the joints which is inhibited when the circulating antibodies in the serum are kept to a low concentration by the anti-rheumatic drugs."

Euphylline

Musser has published the abstracted histories of twenty patients with several types of heart pain (associated with hypertensive heart disease (fatigue pain) in seven cases, with coronary thrombosis in six cases, and with angina pectoris in seven cases) indicating the apparently beneficial effect of theophylline-ethylenediamine (euphylline) given in 0.1 to 0.2 gram doses three times a day. "The greatest value of the drug lies in the treatment of patients with angina pectoris" (shown by a careful observation of thirty patients). "It is only slightly less valuable in the handling of patients who have survived the initial effect of coronary thrombosis."

Thyroid

Drake has recorded a case of high grade auriculoventricular block with Adams-Stokes attacks much improved while taking thyroid extract after barium chloride had failed. The case, a young man aged 29 years, showed cardiac enlargement with probable valvular disease. An electrocardiogram taken a year after he was under observation and treatment for his heart block showed normal rhythm at a rate of 77 with normal A-V conduction and intraventricular block. He was apparently well and was working at his trade as carpenter. He had not continued the thyroid therapy.

Sulphocyanates

Gager has studied the effect of potassium sulphocyanate in 35 patients with essential hypertension. He found the results almost uniformly successful when the patients were co-öperative and the physical obstacles not too great. He believes its use should not supplant fundamen-

tal hygienic and dietary methods, but it deserves further trial.

Smith and *Rudolph* have reported a study of the effect of sodium sulphocyanate in 6 persons with normal blood pressure, and in 72 patients with hypertension, most of them uncomplicated by nephritis. They concluded that

"1. Sodium sulphocyanate causes a fall in the blood pressure, especially in the systolic, with usually no change in the rate of the heart.

"2. This fall occurs when the pressure is normal as well as when it is abnormally high.

"3. In patients showing much kidney damage or arteriosclerosis the effect is least evident but usually occurs to some extent.

"4. The best results are obtained in the large class coming under the heading of 'essential hyperpiesis.'

"5. The sulphocyanates have been observed to have a sedative effect and are often mildly hypnotic.

"6. They are easy to administer and not unpleasant to take in an aromatic mixture.

"7. A dose of 2½ grains twice or thrice daily is sufficient to obtain the effect."

In these cases reported the fall in systolic blood pressure was frequently very pronounced, 50 to 100 mm.

Intrait de gui

O'Hare and *Hoyt* have studied the effect of intrait de gui (2 per cent. solution of the dry extraction of mistletoe in alcohol and water), in the dosage of 2.5 to 5 cc. by mouth three times daily, in 100 cases of vascular hypertension. Of 78 of these cases who complained of the "typical hypertensive headache", 59 (about 75 per cent.) were consistently relieved after three or four days of treatment. Of 35 patients complaining of dizziness, 26 (or about 74 per cent.) were relieved. Of 4 patients with tinnitus 2 were benefited. In 25 per cent. of the cases (18 out of 72) a drop of at least 20 mm. mercury or more in the systolic blood pressure occurred during the administration of the mistletoe. The authors do not attach much significance to this fall of blood pressure since it occurred in so few of the cases.

B. SURGICAL

The problems of surgery of the sympathetic system have continued to occupy many investigators, especially those referable to the surgical control of angina pectoris. Operations upon the cervical sympathetics have been less in evidence in this country at least. *Leriche* and *Fontaine* summarize the situation as follows: "The surgical treatment of angina pectoris seems to be perfectly justified on condition that only carefully diagnosed cases are submitted to it." Contrary to current opinion, they believe that it is indicated in early cases before they become too advanced or too severe, and while the organ can be considered sound. In very severe and far advanced cases, they recommend palliative treatment, such as paravertebral injections of alcohol and procaine. However, "the surgical treatment of angina pectoris still remains open for discussion. The best method is still to be found. Experimental studies on animals are of little value now because they can answer questions of only secondary importance. Real advance along this particular line can come only from greater experience and for this reason we must have very carefully studied observations." "As angina pectoris is not a very common disease, no surgeon can reasonably expect to acquire sufficient surgical experience to answer all of the questions arising in this connection. For this reason all surgeons who have done such operations should publish their complete observations in a precise and uniform manner, so that some day some one may balance the results and arrive at some conclusions as to what is the most satisfactory method to follow in the surgical treatment of angina pectoris."

Richardson and *White* conclude: "(1) The pain of angina pectoris may be modified or abolished by operation on the cervicothoracic sympathetic system, or by paravertebral injection of alcohol. (2) That the relief of pain or interruption of the nervous mechanism of the heart exerts a harmful effect on the course of the disease, although possible, is not proved. (3) Paravertebral injection of alcohol appears safer than operation upon the sympathetic connections of the heart in the treatment of angina pectoris. (4) In carefully selected cases, refractory to other measures, further observations on the effect of paravertebral injections of alcohol are justified.

The use of paravertebral alcohol injections for angina is growing. *James C. White* and *Paul D. White* have reported their experience. "(1) In five of the most severe cases of angina pectoris admitted to the Massachusetts General Hospital during a period of seven months, paravertebral alcohol injections were given in the upper five intercostal nerves on the left side.

"(2) Two patients showed complete relief from the left sided anginal attacks but a continuance of mild to moderate crises on the uninjected side. Two others had their very severe attacks converted into milder and less frequent attacks. The fifth patient was apparently helped only for a few days. To date the relief may be said to be valued at 90 per cent. in one case, 75 per cent. in one, 50 per cent. in one until his death nine months later from coronary thrombosis, 25 per cent. in one and 0 per cent. in one.

"(3) There have not been any harmful complications but all the patients have complained more or less of hyperesthesia of the injected nerves lasting from two to four weeks."

Pletnev and *Hesin* saw good results in cases of angina pectoris from injections of procaine hydrochloride, followed by alcohol, into the first, second and third thoracic ganglions, and, if necessary, also into the fourth thoracic and seventh and eighth cervical ganglions. Injections in the same regions were repeated as often

as six times. Pletnev distinguishes four types of angina pectoris, the cardiac, extracardiac and combined types and sympathicoganglionitis with or without an anatomic basis.

IX. Social and Economic

Clark has written of his considerable experience of the effects of accidents on cardiac employees. He concludes that "as a rule the diseased heart is unaffected by accident, but in a certain number of cases the exception occurs, especially in old workers, who have cardiac disease, or in the case of those who are on the edge of heart failure. There appears to be no special type of accident which is invariably followed by heart weakness and failure."

Commissioner Donahue of the Industrial Accident Board of the Commonwealth of Massachusetts has written on the Court's point of view of the relationship of accidents and heart disease. He discusses the development and work of the Industrial Board of Massachusetts and the Workmen's Compensation Act, citing three fundamental cardiac cases on which legal decisions are largely based,—the Brighton, Madden and Weatherbee cases, the first two in 1914 and 1916 respectively. His experience has been that "accidents are a very important factor in diseases of the heart, that they do contribute to longer disability and in many cases to the death of the employee, particularly among the older employees."

Gleason has discussed the insurance company's point of view of accidents and heart disease in an interesting and useful manner, bringing to the subject his legal knowledge and experience. He begins by quoting Chief Justice Rugg "Acceleration of previously existing heart disease to a mortal end sooner than otherwise it would have come is an injury within the meaning of the Workmen's Compensation Act." He deplores the fact that this Workmen's Compensation Act "makes no distinction between healthy and diseased employees" so that a proper ratio of responsibility may be assigned to the accident with proper compensation, instead of full compensation or none at all such as exists in most states. In Kentucky the law covers this point satisfactorily allowing a proper apportionment of compensation. He ends by reciting three difficult cases.

Halsey has found that although heart disease is the chief cause of death in New York State (exclusive of New York City), ninety per cent. of the deaths from heart disease occur after the age of forty-five, and between the ages of fifteen and thirty-five tuberculosis causes far more deaths than heart disease or any other factor. "Heart disease then appears to be a disease of advanced and old age and it suggests that the prolongation of life may be a factor in the increasing number of deaths ascribed to cardiac disease."

BIBLIOGRAPHY

Aalsmeer, W. C., and Wenckebach, K. J.: "Beriberi Heart." Nederl. Tijd. v. Geneesk., 1928, 1:2340.
Abbott, Maude E.: "Coarctation of the Aorta of Adult Type. II. A Statistical Study and Historical Retrospect of Two Hundred Recorded Cases with Autopsy, of Stenosis or Obliteration of the Descending Arch in Subjects above the Age of Two Years." Am. Heart Jour., 1928, 3:574.
Allan, G. A.: "Diseases of Coronary Arteries." Brit. Med. Jour., 1928, 2:232.
Assmann, H.: "Die Klinische Röntgendiagnostik der Inneren Erkrankungen." F. C. W. Vagal, Leipzig, 1928, Fourth Edition.
Barker, M. H., and Levine, S. A.: "Cardiazol. Effects on Cardiorespiratory Mechanism." Arch. Int. Med., 1928, 42:14.
Barker, M. H., and O'Hare, J. P.: "The Use of Salyrgan in Edema." Jour. A. M. A., 1928, 91:2060.
Bell, E. T., and Clawson, B. J.: "Primary (Essential) Hypertension." Archives of Path., 1928, 5:939.
Benedict, F. G., and Parmenter, H. S.: "Energy Metabolism of Women While Ascending or Descending Stairs." Amer. Jour. Physiol., 1928, 84:675.
Blackford, L. M.: "Coarctation of the Aorta." Arch. Int. Med., 1928, 41:702.
Bloedorn, W. A., and Dickens, P. F.: "Danger of Administration of Ephedrine in Heart Failure." Arch. of Int. Med., 1928, 42:322.
Blumgart, H. L., and Weiss, S.: "Clinical Studies on Velocity of the Blood Flow. XI. The Pulmonary Circulation Time, The Minute Volume Blood Flow through the Lungs, and the Quantity of Blood in the Lungs." Jour. Clin. Invest., 1928, 6:103.
Bourne, C. R.: "Auricular Flutter Restored to Normal Rhythm by Quinidine with Report of Case." Canad. M. A. J., 19: 180-183, 1928.
Boyd, A. N.: "Inflammatory Basis for Coronary Thrombosis." Amer. J. Path., 1928, 4:159.
Bradley, E. B., and Maxwell, E. S.: "Primary Neoplasm of the Heart." J. A. M. A., 1928, 91:1352.
Bramwell, J. C., and Ellis, R.: "Ultimate Results of Quinidine Therapy in Auricular Fibrillation." Lancet, 1928, 2:960.
Brunn, F.: "Cardiac Asthma." Zentralbl f. inn. Med., 1928, 49:873.
Camp, W. J. R.: "Pharmacology of Cardiazol." Jour. Pharmacol. and Exper. Therap., 1928, 33:81.
Campbell, J. S.: "Stereoscopic Radiography of Coronary Circulation." Lancet, 1928, 2:168.
Chang, H. C., and Harrop, G. A., Jr.: "The Determination of the Circulating Blood Volume with Carbon Monoxide." Jour. Clin. Invest., 1928, 5:393.
Christian, H. A.: "Nonvalvular Disease of the Heart." Jour. A. M. A., 1928, 91:549.
Clark, W. I.: "Effects of Accidents on Cardiac Employees." Amer. Heart Jour., 1928, 3:539.
Clawson, B. J.: "Myocarditis." Amer. Heart Jour., 1928, 4:1.
Coffen, T. H., and Carey, H. A.: "Heart Disease in School Children." Northwest Med., 1928, 27:184.
Cohn, A. E., and Stewart, H. J.: "Relation Between Cardiac Size and Cardiac Output per Minute Following Administration of Digitalis in Normal Dogs." J. Clin. Investigation, 1928, 6:53.
Cohn, A. E., and Stewart, H. J.: "Relation Between Cardiac Size and Cardiac Output Per Minute Following Administration of Digitalis in Dogs in Which Heart Is Enlarged." J. Clin. Investigation, 1928, 6:79.
Cutler, O. I.: "Relation of Arteriosclerosis of Cerebral Vessels to Hypertension: Distribution of Arteries Supplying Pons and Medulla." Arch. of Path., 1928, 5:365.
Dandy, W. E.: "Arteriovenous Aneurysm of Brain." Arch. Surg., 1928, 17:190.
Derick, C. L., Hitchcock, C. H., and Swift, H. F.: "Effect of Anti-rheumatic Drugs on Arthritis and Immune Body Production in Serum Disease." Jour. Clin. Inves., 1928, 5:427.
Donahue, F. J.: "Accidents and Heart Disease from the Court's Point of View." Am. Heart Jour., 1928, 3:532.
Drake, E. H.: "Complete Heart Block: Case: Reaction to Drugs." Amer. Heart Jour., 1928, 3:560.
Dumas, A.: "Mitral Stenosis with Hypertension." Presse Med., 1928, 36:1172.
East, D. F. T., Bain, C. W. C., and Cary, F. L.: "Cardiac Infarction Without Pain." Lancet, 1928, 2:60.
Eimer, K.: "Der Einfluss körperlicher Leistungen auf das Herz. Deutsche Med. Wchnschr., 54:174-177, 1928.
Emerson, P. W., and Greene, H.: "Idiopathic Hypertrophy of the Heart in Infants." Amer. Heart Jour., 1928, 4:116.
Fossier, A. E.: "Mechanically Stimulated Ventricular Extrasystoles in Man." J. A. M. A., 1928, 90:1103.
Gager, L. T.: "Incidence and Management of Hypertension with Note on Sulphocyanate Therapy." J. A. M. A., 90: 82-86, Jan. 14, 1928.
Geraudel, E., and Mouquin, M.: "Treatment of Paroxysmal Tachycardia." Paris, Méd., 1928, 2:26.
Gleason, G.: "Accidents and Heart Disease: From Insurance Company's Point of View." Am. Heart Jour., 1928, 3:525.
Grant, R. T., and Jones, T. D.: "Obstruction to Cardiac Coronary Sinus." Heart, 1928, 14:241.
Grant, R. T., and Wood, J. E., Jr., and Jones, T. D.: "Heart Valve Irregularities in Relation to Subacute Bacterial Endocarditis." Heart, 1928, 14:247.
Haberlandt, L.: Hdb. Biol. Arbeits Meth., 1928, Sect. 5, part 8, Heft. 2, p. 237.

Halsey, R. H.: "Observations on Mortality of Heart Disease in New York State." Am. Heart Jour., 1928, 4:94.
Hamilton, B. E., and Kellogg, F. S.: "Cardiac Disease in Pregnancy." Jour. A. M. A., 1928, 91:1942.
Haskell, C. C.: "The Influence of Quinidine on the Cardiac Irregularity Produced by Digitalis." Jour. Pharmac. and Exper. Therap., 1928, 32:223.
Hermann, E. T.: "Status of Quinidine Therapy." Minn. Med., 1928, 11:514.
Hyman, A. S.: "Heart in Mushroom Poisoning." Johns Hopkins Hosp Bull., Balt., 1928, 42:8.
Ionescu, D., Enachescu, M., and Teitel, A. B.: "New Group of Sympathetic Cardiac Nerves." Klin. Wchnschr., 1928, 7:991.
Kaiser, A. D.: "Skin Reactions in Rheumatic Fever (Birkhaug Test)." Jour. of Infec. Dis., 1928, 42:25.
Kampmeier, O. F.: "On the Lymph Flow of the Human Heart, with Reference to the Development of the Channels and the First Appearance, Distribution and Physiology of Their Valves." Am. Heart Jour., 1928, 4:210.
Kauf, E., and Zak, E.: "Störungen des Wasserhaushaltes, insbesonders der Schweiss-Sekretion bei Kreise auf Kranken." Wein. Klin. Wchnschr., 1927, nr. 45.
Keefer, C. S., and Resnik, W. H.: "Angina Pectoris: Caused by Anoxemia of Myocardium." Arch. Int. Med., 1928, 41:769.
Keith, N. M., Wagener, H. P., and Kernohan, J. W.: "Syndrome of Malignant Hypertension." Arch. Int. Med., 1928, 41:141.
King, J. T.: "Clinical Recognition and Physical Signs of Bundle Branch Block." Am. Heart Jour., 1928, 3:505.
Kohan, B. A., and Bunin, E. I.: "Differential Diagnosis During Life Between Coronary Thrombosis of Right and Left Coronary Artery." Ztschr. F. Kreislauf, Dresden, 1928, 20:199.
Kugel, M. A.: "Anatomic Studies on Coronary Arteries and Their Branches. I. Arteria Anastomotica Auricularis Magna." Amer. Heart Jour., 1928, 3:260.
Kugel, M. A., and Epstein, E. Z.: "Lesions in Plumonary Artery and Valve Associated with Rheumatic Cardiac Disease." Arch. Path., 1928, 6:247.
Kurtz, C. M., and White, P. D.: "Percussion of Heart Borders and Roentgen Ray Shadow of Heart: One Hundred Cases." Am. J. M. Sc., 1928, 176:181.
La Barre, J.: "Action of Ephedrine on Anesthetized Animals." Brussels Med., 1928, 9:3.
Laurell, H.: "Roentgenologische Herzstudien." Upsala Lakareforenings Forhandlingar, 1928, 34:496.
Leriche, R., and Fontaine, R.: "Surgical Treatment of Angina Pectoris." Amer. Heart Jour., 1928, 3:649.
Levin, L.: "Angina Pectoris in Children." Am. Heart Jour., 3:495-496, 1928.
Levine, S. A., and Fulton, M. N.: "Relation of Hypertension to Mitral Stenosis." Amer. J. Med. Sci., 1928, 176:465.
Levy, R. L., and Golden, R.: "The Treatment of Rheumatic Carditis by Roentgen Irradiation of the Heart." Am. Heart Jour., 1928, 4:127.
Lewis, T., and Haynal, I.: "Tone of Minute Vessels of Human Skin: Measurement of Pressure Within These Vessels." Heart, 1928, 14:177.
Lincoln, E. M., and Spillman, R.: "Roentgen Ray Studies on Hearts of Normal Children." Amer. J. Dis. of Children, 1928, 35:791.
Ljungdahl, M.: "Chronic Embolism of Plumonary Artery." Deut. Arch. klin. Med., 1928, 160:1.
Marvin, H. M.: "Paroxysmal ventricular tachycardia with alternating complexes due to digitalis intoxication." Am. Heart J., 1928, 4:21.
Matthews, B. H. C.: "A New Electrical Recording System for Physiologic Work." Jour. Physiol., 1928, 65:225.
McMillan, T. M., and Cook, A.: "Electrocardiographic Changes Occurring during Rheumatic Fever." Atlantic Med. Jour., 1928, 31:806.
Mebius, J.: "Edema Theory of Beriberi." Neder. Tijd. v. Geneesk, Haarlem, 1928, 72:3985.
Meixner, K.: "Dilatation of Left Ventricle of Heart in Rachitis." Wien. Klin. Wchnschr., 1928, 41:1273.
Melville, K. I., and Stehle, R. L.: "Mercury Diuresis." Jour. Pharm. and Exper. Therap., 1928, 34:209.
Miller, H. R., and Weiss, M. M.: "Disease of Coronary Arteries Without Gross Cardiac Hypertrophy." Arch. of Int. Med., 1928, 42:74.
Moschowitz, Eli.: "Tobacco Angina Pectoris." Jour. of Amer. Med. Assoc., 1928, 90:733.
Mudd, S. G., and White, P. D.: "The Auscultatory Gap in Sphygmomanometry." Arch. Int. Med., 1928, 41:249.
Müller, F. V.: "The Teaching of Percussion." N. E. Jour. Med., 1928, 199:807.
Musser, J. H.: "Theophylline-Ethylenediamine in Heart Disease." J. A. M. A., 1928, 91:1242.
O'Hare, J. P., Calhoun, A. W., and Altnow, H. O.: "Myocarditis." J. A. M. A., 1928, 90:1436.
O'Hare, J. P., and Hoyt, L. H.: "Mistletoe in Treatment of Hypertension." N. E. Jour. Med., 1928, 199:1207.
Pal, J.: "Gastric Pneumatosis, Hypotonia of Cardia and Angina Pectoris." Wien. klin. Wchnschr., 1928, 41:1116.
Palmer, R. S., and White, P. D.: "The Clinical Significance of Aberrant Response to Auricular Premature Beats and to Paroxysmal Auricular Tachycardia." Am. Heart Jour., Vol. IV, No. 2, 1928, p. 127.
Palmer, R. S., and White, P. D.: "Paroxysmal Ventricular Tachycardia with Rhythmic Alternation in Direction of Ventricular Complexes in Electrocardiogram." Am. Heart Jour., 1928, 3:454.
Palmer, R. S., and White, P. D.: "A Note on the Continuous Humming Murmur, Heard in the Supra and Infra-Clavicular Fossae and over the Manubrium Sterni in Children." N. E. Jour. Med., 1928, 199:1297.
Pardee, H. E. B.: "Clinical Observations on the Use of Intravenous Digitalis Preparations." Jour. Amer. Med. Assoc., 1928, 91:147.
Parkinson, J., and Bedford, E.: "Cardiac Infarction and Coronary Thrombosis." Lancet, London, 1928, 1:4.
Paul, J. R.: "Pleural and Pulmonary Lesions in Rheumatic Fever." Medicine, 1928, 7:383.
Pietnev, D. D., and Hesine, V. R.: "Paravertebral Injections for Angina Pectoris." Klin. Med. Moscow, 1928, 6:797.
Pulgram, F.: "Case of Cysticerosis of Brain and Heart." Wien. klin. Wchnschr., 1928, 41:1088.
Reid, W. D., and Kenway, F. L.: "Value of Electrocardiogram in Acute Rheumatic Fever." N. E. Jour. of Med., 1928, 198:177.
Reinberg, S. A., and Mandelstam, M. E.: "Dextrocardia." Vestnik Roentgen. i. radiol, Leningrad, 1927, 5:349.
Reitzel, R. J., and Stone, C. T.: "Parathyroid Extract-Collip as a Diuretic." J. A. M. A., 1928, 91:1288.
Richardson, E. P., and White, P. D.: "Sympathectomy in the Treatment of Angina Pectoris, Comparison of Results with Those from Paravertebral Alcohol Injection." Am. Jour. Med. Sci., 1929, 177:161.
Ritter, S. A., Gross, L., and Kugel, M. A.: "Blood Vessels in Valves of Normal Human Hearts." Amer. Heart Jour., St. Louis, 1928, 3:433.
Rösler, H.: "Congenital Heart Defects." Wien. Arch. f. inn. Med., Berlin, 1928, 15:478.
Rothman, P. E., and Leonard, B. W.: "Cardiac Failure in Children under Five: Acute Rheumatic Carditis." Am. J. Dis. of Children, 1928, 35:1.
Rukstinat, G. J., and LeCount, E. R.: "Air in the Coronary Arteries." J. A. M. A., 1928, 91:1776.
Scherf, D.: "Zur Theorie des Vorhofflatterns und Vorhofflimmerns." Ztschr. f. d. ges. exper. Med., 1928, 61:30.
Schlesinger, B.: "Subacute Infective Endocarditis in Childhood." Brit. Jour. Child. Dis., 1928, 25:33-48.
Schwartz, S. P., and Weiss, M. M.: "Auricular Fibrillation in Children. Relation to Rheumatic Heart Disease." Amer. J. Dis. of Child., 1928, 36:22.
Scott, L. C., and Herrmann, G. R.: "Beriberi." J. A. M. A., 1928, 90:2083.
Simici, D., and Marcou, I., and Popescu, M.: "Diuretic Action of Urea." Presse Med., 1929, 36:946.
Small, J. C.: "Rheumatic Fever. I. Specificity of Streptococcus Cardio-arthritidis in Rheumatic Fever and Sydenham's Chorea." Amer. J. Med. Sci., 1928, 175:638.
Smith, A. G., and Rudolf, R. D.: "Use of Sulphocyanate of Soda in High Blood Pressure." Canad. Med. Assoc. Jour., 1928, 19:288.
Smith, W. C.: "Ventricular Tachycardia Showing Bi-Directional Electrocardiograms, Associated with Digitalis Therapy." Am. Heart Jour., 1928, 3:723.
Smith, W. C., Burwell, C. S., and DeVito, M. J.: "Effect of Atropine on Output of Hearts of Normal Men." Jour. of Clin. Inves., 1928, 6:237.
Smith, H. L.: "Relation of Weight of Heart to Weight of Body and of Weight of Heart to Age." Am. Heart Jour., 1928, 4:79-93.
Spiro, H., and Newman, W. W.: "Quinidine in Auricular Fibrillation." J. A. M. A., 1928, 91:1268.
Sprague, H. B., and White, P. D.: "Auricular Flutter." J. of Amer. Med. Assoc., 1928, 90:1772.
Stecher, R. M.: "Stokes-Adams Disease Treated with Ephedrine." Amer. Heart Jour., 1928, 3:567.
Stolkind, E. J.: "Angina Pectoris in Children." Brit. J. Children's Dis., 1928, 28:1.
Swift, H. F., Derick, C. L., and Hitchcock, C. H.: "Bacterial Allergy (Hyperergy) to Nonhemolytic Streptococci in Its Relation to Rheumatic Fever." Jour. of Amer. Med. Assoc., 1928, 90:906.
Swift, H. F., and Hitchcock, C. H.: "Cardiac Pain in Rheumatic Fever." Jour. of Amer. Med. Assoc., 1928, 90:678.
Thompson, W. O., Thompson, P. K., and Dailey, M. E.: "Effect of Posture on Composition and Volume of Blood in Man." Jour. of Clin. Inves., 1928, 5:573.
Vaquez, H., and Bordet, E.: "Radiologie du Coeur et des Vaisseaux de la Base." Quatrième Edition entierement refondue, J. B. Bailliere et Fils. 1928, Paris.
Walser, H. C.: "Subacute Bacterial Endocarditis of Streptococcus Viridans Type in Pregnancy." Am. Jour. Obst. and Gyn., 1928, 15:840.
Wassermann, S.: "Zur Pathogenese des Akuten Herzlungenödems." Wien. klin. Wchnschr., 1928, 41:190.
Wearn, J. T.: "Extent of Capillary Bed of Heart." J. Exper. Med., 1928, 47:273.
Weiss, S., and Rhoads, C. P.: "Healing and Healed Vegetative (Subacute Bacterial) Endocarditis." N. E. Jour. Med., 1928, 199:70.
White, James C., and White, Paul D.: "Angina Pectoris: Treatment with Paravertebral Alcohol Injections." Jour. of Amer. Med. Assoc., 1928, 90:1099.
White, Paul D.: "The Clinical Significance of Gallop Rhythm." Arch. Int. Med., 1928, 41:1.
Wilson, C. P., Pilcher, C., and Harrison, T. R.: "Effect of Ephedrine on Minute Cardiac Output of Normal Dogs." Arch. of Int. Med., 1928, 41:622.
Wilson, M. G., Lingg, C., and Croxford, G.: "Statistical Studies Bearing on Problems in the Classification of Heart Disease. II. Heart Disease in Children." Am. Heart Jour., 1928, 4:164.

Case Records
of the
Massachusetts General Hospital

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICO-PATHOLOGICAL EXERCISES

EDITED BY R. C. CABOT, M.D.

F. M. PAINTER, A.B., ASSISTANT EDITOR

CASE 15331

DYSPNEA

MEDICAL DEPARTMENT

A Chinese restaurant manager fifty-three years old entered March 12 *in extremis*. His chief complaint was dyspnea. The history was given by his wife. Its reliability and completeness are questionable.

Except for nocturia for years he had always been perfectly well until five months before admission. Then he began to be dyspneic on exertion, to find that two pillows were more necessary than before, and to have edema of the ankles at the end of the day, passing off at night. After a doctor had put him to bed for two weeks and given him digitalis all the symptoms subsided and the patient returned to work, continuing to take digitalis. He had only occasional edema, slight dyspnea and a tendency to easy fatigue until fifteen days before admission, when his ankles began to swell more than usual. March 1 he vomited, felt weak and ill and had a return of dyspnea. Since that time he had been in bed. March 5 although he was in bed the dyspnea became worse and he had orthopnea. He was put on three digitalis pills a day and other medication. The night before admission he was much worse, delirious, vomited three or four times and breathed heavily, clutching at the clothing at his neck. He apparently had trouble in seeing, as he kept complaining of his glasses.

His wife knew of no familial disease and said that he had no bad habits. His work was not strenuous, although the hours were long.

He had not been ill before in twelve years of marriage. The past history was negative.

Clinical examination showed a well-nourished Chinaman with Cheyne-Stokes breathing, restless during the periods of rapid breathing. There was questionable jaundice of the skin and sclerae. Tongue dry and leathery. Breath somewhat acidotic and ammoniacal. Throat dry. At the left base in the back there were medium moist râles, slightly increased voice sounds, no dullness. Apex impulse of the heart felt; location not recorded. Heart moderately enlarged. Rhythm regular except for a tendency to extrasystoles in runs of 20 to 40. Second sound reduplicated over the whole precordia and very loud. A loud rough systolic murmur heard at the apex and in the pulmonic area. Pulses wiry, with little volume. Blood pressure 200/160. Abdomen not distended. A slightly tender liver felt two centimeters below the costal margin. Pupils pinpoint, equal, regular. Fundus examination showed moderate choking of the discs with considerable exudate; the vessels engorged; several small hemorrhages seen. The examination was difficult because of poor coöperation. Knee jerks normal. Ankle jerks not obtained.

Urine not recorded. Blood: 17,100 leukocytes, 92 per cent polymorphonuclears, hemoglobin 80 per cent, reds 6,290,000. Smear showed definitely abnormal red cells, monocytes, microcytes, tailed cells and nucleated red cells. White cells and platelets normal. Non-protein nitrogen 80 milligrams. Creatinin 2.9 milligrams.

Temperature 99.6°. Pulse 100. Respirations 16.

After a subpectoral infusion the patient was quite active. The blood pressure was 210/180. Venesection was done, but only 150 cubic centimeters of blood was obtained because of the patient's restlessness. The evening of admission he suddenly died.

DISCUSSION

BY RICHARD C. CABOT, M.D.

NOTES ON THE HISTORY

We start with a handicap when the reliability of the history cannot be depended upon. The history is more important than the physical examination.

That is a very common history; a break in compensation restored by rest and digitalis.

You notice that he seems to have cerebral symptoms, which we see rarely in pure heart disease. The persistence of cerebral symptoms such as delirium, gestures of clutching, difficulties in seeing, makes me suspect something else besides cardiac trouble.

NOTES ON THE PHYSICAL EXAMINATION

Patients with Cheyne-Stokes respiration usually are restless during the periods of rapid breathing.

The odor of the breath makes us suspect kidney trouble, which we suspected before because of the cerebral symptoms. Sometimes people say the breath was urinous. They mean ammoniacal. The smell of normal urine is very different from anything you get in a case like this. What we smell is ammonia, which is often manufactured in the body in large amounts in kidney trouble.

What can we conclude from the chest examination? Nothing very definite. It might be early edema at the base of the left lung. We certainly could not say it was pneumonia from the signs given us.

By "wiry pulse" one person means one thing, others other things. It is not a good term. We very seldom see a blood pressure as high as this. That is what they meant I believe by the "wiry pulse."

The report on the fundi makes us think that there is increased intracranial pressure very likely due to edema of the brain, showing up as choked discs just as it does in cerebral tumor.

We notice a high white count and a high red count, the white count probably due to some infectious disease coming on as a terminal phenomenon after he was weakened by some chronic disease which we shall try to diagnose in a minute. The increased red count is due to cyanosis from poor heart action, because the red cells are accumulated at the periphery.

A PHYSICIAN: How do you account for all those irregular cells?

DR. CABOT: I don't know. Cyanosis accounts for the quantitative increase, but would not result in a qualitative change in the shape of the cells. We have to find something else to account for those tailed cells. If he had anemia plus cyanosis it would produce that picture. Cyanosis will crowd the red cells to the periphery, but will not give them that abnormal shape. That is what you find in secondary anemia.

DIFFERENTIAL DIAGNOSIS

Here is a man of fifty-three who had not been sick so far as his wife knew until the last five months. For fifty-two and a fraction years he was well. An illness of about five months we cannot call acute. We have to call it chronic. There was five months' chronic illness, then, characterized chiefly by dyspnea, edema and finally by cerebral symptoms by which he died. If you took away those three things, dyspnea, edema and cerebral symptoms, he would be a well man. When we examine him the outstanding facts are the tremendously high blood pressure, with apparently an odor to his breath suggesting uremia. The heart is enlarged and shows a systolic murmur, as most enlarged hearts do. We have no evidence of any valvular disease. I predict that Dr. Mallory will not show us any valvular disease in this heart, although there was a systolic murmur. The rest of the physical examination aside from the blood and the eye fundi is not important. The eye fundi showed principally the effects of increased pressure inside the skull, probably from edema. We are at a disadvantage in not having a specimen of urine. With the facts before us we ought to say uremia due to nephritis, the chronic hypertensive or vascular type of nephritis, with hypertrophied and dilatated heart, chronic passive congestion of all the organs, which was seen in the three l's, lungs, liver, and legs, and will probably be found also in the three p's, the pleura, pericardium and peritoneum.

Then we have some evidence of a terminal infection, not very much, chiefly this high leukocyte count. I lay stress on that because most people with chronic diseases like nephritis die with some terminal infection, an infection which comes on because the body is so weak that it cannot resist invading organisms. We turn back therefore to our general pathologic knowledge. What is the commonest of all terminal infections? Pneumonia. Next to that in nephritic diseases? Pericarditis. Are there any signs of it? None whatever. Can we prove it? Not at all. There are no reliable physical signs of acute pericarditis. We cannot say more. Pneumonia is a little more common, a little more probable when there are no physical signs of any kind.

We have tailed cells which we still have to account for. Why shouldn't he have an anemia masked by cyanosis? The anemia would be shown up by the qualitative changes in the cells. That is my guess. It cannot be more than a guess. We expect anemia in any type of chronic nephritis. The vascular type is much more common in men of this age.

A PHYSICIAN: Isn't interstitial the other name?

DR. CABOT: It is one of the other names. We do not like the word interstitial. It is not characteristic so far as I know in any type of renal disease. This disease so far as we know begins in the vessels and extends from them to other parts of the kidney.

A PHYSICIAN: There was a 92 per cent polymorphonuclear count. Didn't that white count show something more than the results of cyanosis?

DR. CABOT: Yes. The red cells are increased by one-sixth. The white cells are doubled. 92 per cent polymorphonuclears is a qualitative change and points therefore to something more than passive congestion.

A PHYSICIAN: Did he have myocarditis?

DR. CABOT: No, not so far as I know. Myocarditis means (a) abscess or (b) infarction or coronary disease and its results. Abscess of the myocardium is very rare. We have no reason to suppose cardiac infarction.

A PHYSICIAN: How do you account for the vomiting?

DR. CABOT: By uremia, according to my diagnosis. If Dr. Mallory says he did not have uremia or kidney trouble I shall be left in the cold.

A PHYSICIAN: Isn't the respiration of 16 against pneumonia?

DR. CABOT: Yes, it is against it, but I do not think it throws it out. I have seen pneumonia with a respiration of 16, although it is unusual.

MISS PAINTER: He was having morphia.

DR. CABOT: Morphia depresses the respiration even in pneumonia.

A PHYSICIAN: You say he has no valvular disease?

DR. CABOT: Yes.

A PHYSICIAN: He has no symptoms of valve

disease or myocarditis; still you assume that he has a failing heart. Why?

Dr. Cabot: Hypertensive heart disease goes with normal valves, with physical symptoms of dyspnea, orthopnea and all that he has. Hypertrophy tends to push the blood around the circle, but the heart muscle is not strong enough in spite of hypertrophy to overcome the hypertension. The heart tires and fails.

A Physician: What about the pinpoint pupils?

Dr. Cabot: When a man is very sick it does not matter what his pupils are. When I was a house officer here we were always looking at pupils in dying people. It now seems to me a waste of time.

A Physician: What is the difference between this blood and the blood of acute leukemia?

Dr. Cabot: The difference is that he has 92 per cent polymorphonuclears. We never have that in acute leukemia.

CLINICAL DIAGNOSIS (FROM HOSPITAL RECORD)

Chronic nephritis with hypertension.
Hypertensive heart disease.
Uremia.

DR. RICHARD C. CABOT'S DIAGNOSIS

Chronic vascular nephritis.
Uremia.
Hypertrophy and dilatation of the heart.
Chronic passive congestion of all the organs.
Terminal infection, probably pneumonia.
Anemia.

ANATOMIC DIAGNOSES

1. *Primary disease.*

Generalized arteriosclerosis, arteriolar type.

2. *Secondary or terminal lesions.*

Hypertrophy and dilatation of the heart.
Infarct of the lung.
Chronic passive congestion.

Dr. Tracy B. Mallory: I am afraid I cannot entirely agree with any of the diagnoses presented, though I am not sure mine are right. On one point I agree. The man had primarily arteriosclerosis. The question is in which particular organ it was most marked.

The kidneys at post mortem weighed 327 grams. That is a fairly good weight, slightly below normal but not greatly. The capsules stripped with some difficulty and left a finely granular surface, but the cortex was not greatly thinned. The arterioles were widely and diffusely involved, but there was comparatively little extension of the process to the glomeruli. I should not expect the man to show uremia from those kidneys. One other possible explanation of his cerebral symptoms of course would be arteriosclerosis in the brain, and that was found, rather diffuse, without any lesion that could have given localizing symptoms, no softening, no hemorrhage. There was an actual thrombus in one area, but it was not sufficient completely to obstruct the circulation, so that no actual softening was produced.

The heart was enormously hypertrophied and all the cavities were dilated. Except for a slight degree of arteriosclerosis there were no valvular lesions of functional significance. One of the coronary arteries showed quite marked narrowing, but not sufficient to cause occlusion.

My feeling is that it is a case of very widespread, diffuse arteriosclerosis throughout the body, involving the brain, kidneys and heart in approximately equal proportions.

There was some fluid in each pleural cavity, 400 cubic centimeters on the left, 200 cubic centimeters on the right. There was an infarct in the right lower lobe approximately 3 centimeters in diameter, and I think that was probably the reason for the leukocytosis.

Dr. Cabot: What did the heart weigh?

Dr. Mallory: It was not weighed, but I should estimate it at 700 grams perhaps.

Dr. Cabot: What would you say is the average weight for an adult man?

Dr. Mallory: This was rather a stout man. His heart would normally have weighted about 350 grams. It was nearly double the normal size.

Dr. Cabot: What was the cause of death?

Dr. Mallory: It was myocardial failure I suppose.

Dr. Cabot: That is, his heart quit, which is the reason most people die.

A Physician: How about that odor?

Dr. Mallory: I cannot explain that, or the peculiar findings in the blood smear.

Dr. Cabot: I do not think we differ much. Dr. Mallory's findings are compatible with our diagnosis of hypertension. He says also chronic nephritis, but that he should be surprised if it caused uremia. Chronic nephritis produces uremia, and the patient, not the pathologist, determines how much nephritis is necessary to produce uremia. With such things as this patient had, with so high a non-protein nitrogen and creatinin, with such a breath, it seems to me that Dr. Mallory must agree that it might be uremia. You do not say it could not be?

Dr. Mallory: I doubt a little bit if it was. I might say that the hospital diagnosis entirely agrees with yours.

Dr. Cabot: Which means that other clinicians reasoning in the same way came to the same conclusion.

Dr. Mallory: One point of interest is that a certain degree of kidney insufficiency can be produced by cardiac insufficiency of a temporary character. A man with kidneys of this type I should not expect to show renal insufficiency as long as his heart kept going. This type of vascular nephritis plus cardiac failure might result in fairly acute renal insufficiency.

A PHYSICIAN: What is the difference between a nephritis like this and myocarditis?

DR. CABOT: Myocarditis means abscess in the heart wall or fibrous tissue in the heart wall, a perfectly definite thing of which we have not found any evidence. It is a very bad term. Dr. Mallory found a big heart and that was all. A big beefy heart does not mean myocarditis.

A PHYSICIAN: Wouldn't the vomiting be a perfectly good sign of uremia?

DR. CABOT: Dr. Mallory would say that the vascular condition of the brain would produce vomiting. It is hard to prove uremia. We could say that the heart gave out, thereby causing congestion of the kidney on top of some renal insufficiency due to some kidney disease. That is a good way of putting it. After having seen this post mortem should you think that he had a quite diminished urinary output?

DR. MALLORY: One can only guess as to that; but this is the type of kidney we ordinarily see in men with a large dilute urinary output, with a slight degree of inability to concentrate, but ordinarily no nitrogen retention until very late in the game. They usually die of cerebral hemorrhage or heart failure before the kidney shuts down. There are some cases of vascular disease of the kidney in which the renal lesion progresses so fast that the patients die of uremia before the secondary changes take place in the heart or brain. Those are distinctly uncommon, perhaps one to ten cases of the hypertensive type.

A PHYSICIAN: Could this be termed more the malignant type of hypertension than acute nephritis?

DR. MALLORY: Yes, I think we could use that term.

DR. CABOT: Ordinarily the malignant type of hypertension is judged by the findings in the fundi.

A PHYSICIAN: Do we know the condition of his radials?

DR. MALLORY: His external arteries did not show any arteriosclerosis. It is unusual to have the large arteries show any degree of arteriosclerosis. It is essentially a disease of the little arteries, the microscopic arteries. If you can examine the retinal arteries the condition in them very closely parallels the condition in the other arteries.

A PHYSICIAN: What kind of kidneys should we have with this clinical picture?

DR. MALLORY: I should expect a pair of kidneys weighing 150 grams at most before there would be any likelihood of their producing uremia.

DR. CABOT: Underscore once more normal valves with a loud systolic murmur. When I throw out systolic murmurs as I do in clinical cases it is because I have seen so many cases like this.

A PHYSICIAN: What does the high diastolic blood pressure mean?

DR. CABOT: It means that the circular muscles of the arteries are gripping in on their contents from some chemical stimulus in the blood itself. We can have it with no nephritis, no arteriosclerosis. If it lasts long we get one or more of those things. I think hypertension is usually the primary, essential thing, which means we do not know its cause. My guess about this man,—only a guess, because we saw him only at the end,—is that as the hypertension went on it began to produce arteriosclerosis just such as Dr. Mallory describes. I know you can have essential hypertension and normal kidneys and no arteriosclerosis.

A PHYSICIAN: Can you get coronary arteriosclerosis with a heart of normal size?

DR. MALLORY: You can, certainly.

DR. CABOT: I remember cases where there was practically no other arterial disease in any other part of the body, though the coronaries were markedly diseased. By essential hypertension I mean that hypertension for which we find no cause and which, outside of the heart, is associated with no other important lesions. Essential hypertension can be proved only when a man dies at such a stage of the game that no trouble has developed in his heart, his kidneys, or his brain. Dr. Mallory thinks this is not such a case. My belief is that there was a long stage when this man was feeling perfectly well, when if he had been run over and killed we should have found the hypertension but the kidneys and arteries would have been normal.

A PHYSICIAN: Do you believe the muscular tone of that heart was damaged?

DR. MALLORY: I think that that is impossible to answer. We have not the slightest knowledge as to why the heart stops beating in the vast majority of cases.

A PHYSICIAN: Do you think the concentration of urine occurs in the glomeruli?

DR. MALLORY: That is a pretty long question to answer. It is ordinarily assumed that, according to Richards at Pennsylvania, it depends chiefly on whether the tubules concentrate the urine or not, whether their function is or is not suppressed. On that depends the specific gravity of the urine. That does not check very well with the histologic findings of glomerulonephritis.

CASE 15332

FEVER AND LOSS OF WEIGHT OF UNKNOWN ORIGIN

SURGICAL DEPARTMENT

A married American woman of fifty-eight entered May 14 complaining of nausea of three months' duration.

For four years certain foods had caused a "burning" sensation in her stomach as soon as she had eaten them. At first soda relieved this. For a long time it had given no relief. For six

months she had felt sleepy all the time, and dropped asleep so easily that for a week she had been unable to read a paper. Four months before admission she noticed a definite falling off in her appetite. For two months she had been unable to eat anything but crackers and milk. Her chief trouble at admission was nausea. She had constant dull ache between her shoulder blades during the day. A month before admission she had dull pain over her heart and beneath her left breast for two weeks. During the past two weeks she had rapidly grown weak. Her hands and feet felt cold all the time. She often had painful cramps in her hands. She had profuse sweating of the hands and the middle of her back every night. May 5 she felt so weak that she stayed in bed all day, had cyanosis of the lips, could not eat because of nausea, and had three gray stools. The next day she felt better and her stool was normal. She now drank no water because it "burnt her stomach." She passed not more than a pint of urine a day. During the past six months she had lost thirty pounds.

Her father and two brothers died of heart trouble, a third brother of tuberculosis, a sister of cancer.

The patient had the minor diseases of childhood. Twenty-six years before admission she had an ectopic pregnancy. For fifteen years she had had hemorrhoids that bled rarely. Ten or twelve years before admission she had erysipelas three times. For four years she had had dyspnea on exertion and for the past year palpitation on exertion and excitement.

Clinical examination showed a rather obese woman sleeping placidly. Heart and lungs normal. The abdomen showed diffuse tenderness over the upper half and slight spasm to deep palpation. There was a sensation as of many masses, but superficial, as if in the abdominal wall. Extremities, pupils and reflexes normal.

Before operation amount of urine not recorded, specific gravity 1.018 to 1.030, a slight to a large trace of albumin at two of nine examinations, no bile, leukocytes at seven of nine sediment examinations (no catheter specimen). Renal function 50 per cent. Blood before operation: 14,200 to 22,000 leukocytes, 50 to 78 per cent polymorphonuclears, hemoglobin 80 to 65 per cent, reds 4,850,000, slight achromia and variation in size, platelets slightly increased in one of two smears. Hinton negative. Blood culture, no growth. Stools clay colored at one of four examinations, cream colored once. Fasting contents of stomach: 11 c.c. of watery material, no free acid or total acid, guaiac negative. Test meal: 29 c.c., watery, free acid 40 c.c., total acid 62 c.c., guaiac negative. Basal metabolic rate +2, pulse 69, weight 75.8 kilos.

Before operation temperature 97.3° to 103.3°, pulse 64 to 100, respirations normal.

X-ray examination with a barium meal showed no evidence of organic disease of the stomach or duodenum. Examination at twenty-four hours showed delay of the barium in the cecum and the ascending colon. There was suggestive constriction and irregularity of the transverse colon near the hepatic flexure in the region of the tenderness and the questionable mass. Examination with a barium enema showed no evidence of pathology in the colon. The lung fields were clear. The heart shadow was not remarkable. There were no mediastinal masses. Plates of the pelvis, the long bones and the kidney region showed no definite evidence of pathology.

May 17 a very large, hard, tender mass was felt in the right upper quadrant. May 25 it remained unchanged.

A urologist obtained a history of hematuria a year before admission, and offered to make a pyelogram. A surgeon advised operation. June 1 it was performed.

Discussion

BY EDWARD L. YOUNG, JR., M.D.

As we read over this history, the problem comes down to the cause of a persistent septic temperature plus weakness and loss of weight.

The digestive symptoms suggest trouble in the stomach, duodenum, or biliary tract. The clay colored stool that was noticed in the hospital is suggestive of biliary tract obstruction, but there is no note of jaundice or bile in the urine to go with it. The tenderness and spasm are also indicative of infection in the gall bladder or liver but are not final evidence. The type of temperature which she had, the so-called "picket fence", generally means a suppurative or active infectious process somewhere. The X-ray examination seems to rule out any disease of the stomach or duodenum, and the irregularity near the hepatic flexure is one more link in the chain of evidence pointing toward gall bladder. The inability to find any other focus of trouble and the persistence and severity of her symptoms justified exploration. This is made doubly necessary by the development of the large, hard, tender mass in the right upper quadrant. The mere fact that this patient has lost weight does not prove malignancy, because sepsis alone, and especially sepsis with an inadequate food intake, will do the same thing. Any case where there is persistent temperature which cannot be explained on any diagnosis should always arouse suspicion of biliary tract disease, as this can cause a long continued fever without local symptoms consistent with the severity of the temperature.

In this case, operation showed that the trouble was in the gall bladder, and the description of the gall bladder is entirely adequate to explain all the symptoms, and its removal ought to relieve the situation.

PRE-OPERATIVE DIAGNOSIS JUNE 1

Gall bladder disease?
Carcinoma?
Kidney disease?

FIRST OPERATION

Spinal novocain. Right upper rectus incision. On opening the abdomen a very large, much thickened gall bladder was found, with a large stone impacted in the cystic duct. This was dissected free with much difficulty, as the common duct was lying over the lowest stone. A cigarette wick was placed in the region of the gall bladder.

FURTHER HISTORY

There was drainage of large quantities of bile for the first few days, then only a small quantity. Tenderness to the left of the incision persisted, with some induration. The patient continued to run a widely swinging temperature as before operation, with little to explain it. June 10 there was tenderness to the right of the incision. She continued in the same condition. June 21 X-ray showed the diaphragm high and sharply domed on the right, rising as high as the angle of the scapula. Above it there was some increased density in the lung tissue.

June 26 a second operation was done. Two days later the temperature was lower. June 29 a third operation was done. The patient looked badly after it. The temperature continued to show irregular high swinging until June 9. After that it did not go above 100.3° July 12 the patient was discharged.

FURTHER DISCUSSION

To the surprise of everyone the pathologic report after the first operation came back showing a diffuse malignancy of the gall bladder. This is one of the cases in which it seems very certain that carcinoma has developed on a basis of chronic irritation of a stone. It was obvious that the malignant growth had not been removed entirely, as the operation had been difficult and some of the tissue must necessarily have been left at the stump of the cystic duct. Even at that, however, her temperature should have come down. But it did not. Three weeks after operation X-ray showed a high right diaphragm. The chest examination backed up the probability of trouble in that neighborhood. It seemed almost certain that there was a subdiaphragmatic abscess which accounted for this picture and for the persistent temperature. Accordingly a few days later a section of the tenth rib was removed and the pleura sutured as a preliminary to opening this abscess. Three days later, under local anesthesia, the diaphragm was incised, the perinephritic tissue exposed first to rule out pernephritic abscess, and then the subphrenic area explored. No pus was found, but the under surface of the diaphragm was studded with nodules from the size of the head of a pin to the size of a large pea. Although this has never been recognized as a cause of such an X-ray picture, it seems entirely reasonable to believe that it had in fact caused enough irritation to make the trouble. Following this operation the patient looked badly for a while, but the temperature slowly came down, the patient gained in strength, and she was discharged to a convalescent home. Of course the outlook is ultimately bad.

DIAGNOSIS

Cholelithiasis.
Adenocarcinoma of the gall bladder.

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Communications should be addressed to The New England Journal of Medicine, 126 Massachusetts Avenue, Boston, Mass.

THE THIRTEENTH INTERNATIONAL PHYSIOLOGICAL CONGRESS

THE JOURNAL offers a very warm welcome to the members of the Thirteenth International Physiological Congress who are to meet next week in Boston. As it is the first time that such a congress has gathered in America we think it particularly fitting that the oldest laboratory of physiology for students in this country should have become the host of the occasion. In the fifty-eight years that have elapsed since Henry Pickering Bowditch returned from Leipzig to set up his laboratory at the Harvard Medical School, physiology has progressed with surprising rapidity both in this country and abroad, and the attendance at these international gatherings tells the story of its growth. From a handful of people at the first Congress in Basle in 1889, the numbers have grown each year (except for the first Congress after the War held in Paris in 1920). At the Edinburgh meeting in 1923 there were 516 members, 159 of whom read papers, and at Stockholm 651 members and 238 papers. For the present meeting 1239 members have registered as THE JOURNAL is going to press, 558 from abroad and 681 from the United States and Canada. About 600 members are to present papers, 55 of which are to be read by title. Even so the program is so large that six groups of communications each limited to ten minutes will proceed simultaneously for four successive days (August 20th to 23rd). There were 19 nationalities represented at Paris, 27 at Edinburgh, 33 at Stockholm and 40 are expected in Boston. The majority of the foreign members are arriving on Sunday the 18th, on the S. S. Minnekahda. Elaborate plans, the details of which may be studied on application to the Secretary of the Congress, have been made for entertaining those who attend. There will be a general reception Monday evening at Sanders Theatre in Cambridge, entertainments during the week, and various excursions after the meetings are over.

The president of the Congress, Professor William H. Howell, of Baltimore, and Professor Walter B. Cannon who is chairman of all arrangements, are making every effort to fulfill the aims originally set forth by Sir Michael Foster on the occasion of the first Congress: "to do our best to make it as informal as possible, so that we may freely and without reserve exchange opinions." The meeting will afford an unusual opportunity for the interchange of scientific ideas between physiologists of different nations, and the influence of this upon the advancement of medical science will be, as it has been in the past, salutary and far-reaching.

LIQUOR AND DRUG ADVERTISEMENTS

ADVERTISEMENTS for the cure of the liquor and drug habits are so prevalent in this country and so plausible in their context that it is difficult for persons not trained in medicine to evaluate their importance. It seems necessary that, in some way, physicians and medical journals should present the subject to publishers in a way that cannot be misunderstood. It is interesting to note that the publishing industry and such organizations as the National Better Business Bureau, Inc. have held conferences with the Federal Trade Commission in regard to the censorship of this type of advertising. The Business Bureau now turns to the physicians and asks a number of questions in regard to these types of so-called "cures". For instance, they wish to know if alcoholism can be considered as a "disease". There are many grades of alcoholism. In its early stages, it would certainly be considered as a habit; later, the habit may become fixed and as such might be considered as pathological and therefore a disease; in still later stages, when secondary mental changes take place, alcoholism should rightfully be considered as a cause of one type of psychosis.

It is not worthwhile, however, to dilate too much on a definition. The important thing, from the advertiser's point of view, is the question of whether the habit can be safely and

permanently cured at home by the use of internal medicine. We can definitely answer here that no disease of psychogenic origin, such as alcoholism, is cured by any medicine. The alcohol habit can only be cured by the patient himself, exactly the same as any other habit is stopped. The cure must be in large part voluntary, although much can be done by removing the source of the patient's habit. In other words, withdrawal of alcohol, prevention of access to it, the building up of a man's morale, which has usually been severely shaken by prolonged alcoholism, will cure a certain number of cases. Tendencies to relapse, however, are notorious for, like any other of our habits, either good or bad, we hate to give them up and we resent any interference with what we like to call our "personal liberty".

Drug cures, however, are in a somewhat different category. Here one may substitute, at least temporarily, a drug of lesser habit formation in order to rid the patient of a stronger one. On the other hand, the principles of curing a disease of psychogenic origin should apply to drugs exactly as they apply to alcoholism. One must have a patient, for successful cure, under very strict surroundings, where temptation is removed, a spirit of co-öperation can be developed, and in a place where the patient may see and talk with others who have been cured by a similar course of treatment. It would be most unusual to be able to carry out a successful drug or alcohol cure in the home. Certainly not one patient in 1,000 would be able to cure himself at home by taking some internal medicine.

PHYSICAL EXAMINATION OF AIRPLANE PILOTS

UNDER the Federal Department of Commerce there is an Aeronautics Branch, which has a medical section. This section supervises the physical conditions of pilots of airplanes.

During the past fifteen years concentrated study has been devoted to the physical demands of flying and it is recognized that flying demands high-grade physical preparedness. This means that specially qualified physicians have to conduct physical examinations of prospective pilots, of a technical nature not required for determining the fitness of a person to engage in other pursuits. Although the usual physical examination may not reveal defects, additional investigations of the qualifications of pilots are considered necessary in order to be assured of stability of the nervous system, especially that quality which may be spoken of as reliable equilibrium and a "motion mechanism". The pilot must have good vision both far and near with accurate color perception, eye muscle balance as found in co-ördinate efficiency of both eyes.

Standards are not the same for all classes of pilots, the highest being for those who have the responsibility of passengers and the lowest for the private pilot. The student must pass the private grade at least.

Another very important provision is that a re-ëxamination is required before each renewal of a license. In the highest grade this renewal must be every six months. If an accident occurs the pilot is checked up by a special examination.

These examinations are conducted by physicians selected by the Department of Commerce. All examination reports are sent to Washington and are accepted or rejected by the Medical Section. Over 2500 examination reports are received every month. Over 31,000 have been received in the last nine months. The number seems to be steadily increasing. Aviation medicine is a specialty which is being recommended for inclusion in the curricula of the better medical schools.

The public can feel assured that if a plane is licensed, the pilot is also licensed and that both plane and pilot have met the requirements.

These somewhat elaborate requirements are for the purpose of securing safety to all concerned and incidentally to encourage the further development of aviation as a service to humanity.

This careful supervision of the plane and its pilot will undoubtedly be duplicated in a lesser degree in the requirements for licensing automobiles and their drivers in the not distant future. The person who is killed in an automobile accident is as much a loss to the nation as though he had fallen from the clouds. If one class is to be protected, why not the other? The magnitude of the automobile problem may be equalled by that of the airplane in a few years. Greater miracles will be shown future generations than any thus far recorded.

THE FIFTEENTH ANNUAL REPORT OF THE PETER BENT BRIGHAM HOSPITAL

The usual hospital report consists chiefly of tables; there are tables of surgical diagnoses and of medical diagnoses, of the nationality of patients treated, of the cost of feeding these patients and of the cost of medical supplies. The heads of each service write short, more or less perfunctory reports in which they express their appreciation of the work of the junior members of their departments and let it go at that.

The annual report of the Peter Bent Brigham Hospital is different. It contains, it is true, a number of tables of diagnoses, and tells the cost of raw food per patient. We note with interest that for 1928 this cost $0.48 per day whereas in 1927 it was $0.48+. There the resemblance ceases.

The report is different because it contains a real discussion of the problems which confront not only this hospital, but all hospitals. For this

reason it is not merely a series of statistics, but is a contribution to medical literature.

Anything that Dr. Cushing writes is sure to be well presented as well as stimulating. Appreciation of his literary ability has been expressed before in these columns. The report of the Surgeon-in-Chief in the Peter Bent Brigham Hospital report does not depart from this rule. Dr. Cushing's observations upon hospital affairs touch upon widely diversified matters. In referring to the custom of singing carols on Christmas morning, he steps aside long enough to advise all young medical men to cultivate a hobby, such as music or drawing. In a few words, he makes us feel that those of us who lack these graces are outside the pale. He discusses the "House Plan" for hospitals, a plan which aims to divide medical students among the affiliated hospitals in such a way that each group will do all its hospital work in the same institution, threby bringing about a closer acquaintance between members of the hospital staffs and the students. He urges the establishment of a Harvard Medical School Bulletin in which may be published the results of investigations carried on at the School and affiliated hospitals. In addition to the discussion of these and other subjects, he reviews briefly the latest developments in the careers of his junior surgeons.

In the report of the Physician-in-Chief, Dr. Christian discusses first the neglected opportunities in hospital services for the education and development of house officers and residents. He advocates a larger ratio of internes to patients and a lightening of the clerical labor demanded, so that the men may have more time for investigation and reading. Several pages are devoted to a discussion of the value of dental hygiene; Dr. Christian would have a salaried part-time dental surgeon and full-time assistant appointed to care for the teeth of patients not only from the point of view of cleanliness but from that of improved mastication as well. The problems of the Out-door Department are considered in his report, and once more, as in his report for 1926, he advocates the establishment of a single diagnostic service instead of separate medical and surgical services.

Such criticisms as these apply to all hospitals. They stimulate us and lead us to wonder whether, after all, the systems which have been followed for so long may not be susceptible of improvement. The annual hospital report is an excellent medium for the presentation of such ideas.

THE PROCRASTINATING PARTICIPANT IN THE SECTION MEETINGS

Immediately after the annual meetings of the Massachusetts Medical Society, the Journal plans for the publication of the proceedings of the scientific sections but one or more doctors, among those who have read papers or discussed the subjects presented, do not return the stenographic reports or the galley proofs promptly. Although the meetings were held more than two months ago, no section material is at this time ready for publication and much of the material has been in the hands of authors for some time.

It seems difficult to make some authors realize their responsibility to the Society and their associates in section work. The interest in Society transactions wanes with the lapse of time.

THIS WEEK'S ISSUE

Contains articles by the following named authors:

Walker, Irving J. A.B., M.D. Harvard 1907. F.A.C.S. Clinical Professor of Surgery, Harvard Medical School; Surgeon-in-Chief, Fifth Surgical Service, Boston City Hospital. He writes on: "Carcinoma of the Head of the Pancreas." Page 291. Address: 520 Commonwealth Ave., Boston.

Jackson, Henry Jr. A.B., M.D. Harvard 1919. Associate, Thorndike Memorial Laboratory, Boston City Hospital; Junior Visiting Physician, Boston City Hospital; Senior Visiting Physician, Pondville Hospital; Assistant Physician, C. P. Huntington Memorial Hospital; Physician to Tumor Clinic, Beth Israel Hospital; Instructor in Medicine, Harvard Medical School. He writes on: "Recent Advances in the Biology of Cancer." Page 294. Address: Boston City Hospital, Boston.

Allen, Arthur W. A.B., M.D. Johns Hopkins Medical School 1913. F.A.C.S. Associate Surgeon, Massachusetts General Hospital; Instructor in Surgery, Harvard Medical School. He writes on: "The Surgical Treatment of Embolism of the Extremities." Page 304. Address: 264 Beacon St., Boston.

Branch, Charles F. M.D. University of Vermont 1923. Associate Professor of Pathology, Boston University School of Medicine; Pathologist to Massachusetts Homeopathic Hospital and Framingham Union Hospital; Associate in Pathology, Evans Memorial Hospital; Consulting Pathologist to Newton Hospital and Waltham Hospital. He writes on: "A Bacteriological Study of a Group of Diseased Gall Bladders." Page 308. Address: 80 E. Concord St., Boston.

Sprague, Howard B. A.B., M.D. Harvard 1922. Assistant Physician Massachusetts General Hospital; Assistant in Medicine; Harvard Graduate School of Medicine; Visiting Physician, House of the Good Samaritan. He writes on: "Progress in the Study of Cardiovascular Disease in 1928." Page 313. Address: 270 Commonwealth Ave., Boston.

MISCELLANY

REPORT OF MARCH, 1929, EXAMINATIONS CONDUCTED BY THE MASSACHUSETTS BOARD OF REGISTRATION IN MEDICINE

Names of Schools Conferring Degrees	No. Registered	No. Rejected
Tufts Medical School	5	
Kansas City University of Physicians and Surgeons	2	3
Middlesex College of Medicine and Surgery	2	11
University of Athens		2
Laval		1
College of Physicians and Surgeons, Boston	1	1
Massachusetts College of Osteopathy	2	9
DesMoines Still College of Osteopathy and Surgery		2
Kirksville College of Osteopathy and Surgery	3	1
Missouri College of Medicine and Science	3	3
University of Montreal	2	
Philadelphia College of Osteopathy	1	2
Royal University of Padua	1	
Harvard	10	
Montreal Medical School	1	
Boston University Medical School	1	
Queens Medical School	1	
University of Virginia	2	
St. Louis University	1	
Los Angeles College of Osteopathy and Surgery	1	
Cornell	2	
Rush Medical School	2	
Columbia College of Physicians and Surgeons	1	
Johns Hopkins	2	
Coimbra University	1	
St. Louis College of Physicians and Surgeons		1
	47	36

Total number examined 83
Total number registered 47
Total number rejected 36

Candidates Registered in the March, 1929, Examination

Aguglia, Vincent Bellini, 232 Hanover Street, Boston.
Albert, Samuel Martin, Bridgeport Hospital, Bridgeport, Conn.
Belson, Maurice Abraham, Long Island Hospital, Boston.
Benson, Hilda Florence, 2 Westland Avenue, Suite 14, Boston.
Breen, John Joseph, 39 Wellington Avenue, Lowell.
Brown, Samuel, St. Luke's Hospital, Fall River.
Buttafuoco, Vincenzo, 260 Hanover Street, Boston.
Caron, Gerald Hamelin, No. Reading State San., No. Wilmington, Mass.
Chute, Richard, 350 Marlborough Street, Boston.
Cohen, Samuel, 1133 Columbus Avenue, Roxbury.
Connors, Thomas Aquinas, 317 Common Street, Watertown.
Coolidge, Thomas Buckingham, Massachusetts General Hospital, Boston.
DePrizio, Carl January, Boston City Hospital.
Dixon, Stanley Roderick, Danbury Hospital, Danbury, Conn.
Duckett, John Warner, Children's Hospital, Boston.
Fay, John Howard, Massachusetts General Hospital, Boston.
Fisher, William Howard, 1181 Centre Street, West Roxbury.
Griswold, Marion, 40 Avon Street, Wakefield.
Halbersleben, David Lucian, Peter Bent Brigham Hospital, Boston.
Hallett, Ronald Payne, 36 E. 40th Street, New York City.
Hoskins, Roy Graham, 17 Weldon Road, Newton.
Johnson, Charles Isaac, 243 Charles Street, Boston.
Johnson, David William, Grasslands Hospital, Valhalla, N. Y.
Kidder, Elizabeth Meriel, 53 Conant Street, Beverly.
Kimberly, Charles Hazard, Massachusetts General Hospital, Boston.
Krobalski, Joseph, 120 So. Common Street, Lynn.
Kubik, Charles S., 99 Revere Street, Boston.
Landry, Ernest, Westfield State Sanatorium.
Lapierre, Joseph Charles, Crownsville State Hospital, Waterbury, Md.
McPeak, Clarence Nuckolls, Massachusetts General Hospital, Boston.
Magid, Beatrice, 43 Evergreen Street, Jamaica Plain.
Mahoney, Joseph Aloysius, 32 Forbes Street, Worcester.
Marble, Alexander, Massachusetts General Hospital, Boston.
Martindale, Richard Edward, 171 Westminster Street, Providence, R. I.
Parkhurst, Irving Wright, Boston City Hospital.
Pereira, Manuel Caetano, 189 Essex Street, Fall River.
Ronchese, Francesco, 235 Marcy Street, Southbridge.
Roscoe, Alfred Mortimer, Boston City Hospital.
Siegel, Max, care of Henry Bletzer, 2090 Walton Avenue, Bronx, N. Y.
Stern, Morton Samuel, Beth Israel Hospital, Boston.
Stewart, Ann Hoague, 100 Chestnut Street, Boston.
Summers, Arthur Warren, 1626 Massachusetts Avenue, Cambridge, Mass.
Wakefield, Arthur Paul, 6 St. John's Road, Cambridge.
Weisenfeld, Irving, 131 Bloomingdale Street, Chelsea.
Wetherbee, Richard Meserve, 60 Wendell Street, Cambridge.
Young, Albert Gayland, 5 Everett Street, Cambridge.
Yule, William Lorne, State Hospital, Cleveland, Ohio.

Registered on Certification by the National Board Since Last Report

Hopkins, Edward Baldwin, 24 Washington Street, Ayer.
Worcester, Blandina, 186 Marlborough Street, Boston.
Beetham, William Parks, 2 Arlington Street, Boston.
Schlesinger, Monroe Jacob, 32 Ransom Street, Brighton.
Gregg, Ralph, 67 Hudson Street, New York City.

Harper, James Durfee, Massachusetts Eye and Ear Infirmary, Boston.
Epstein, Samuel Hyman, 33 Moraine Street, Jamaica Plain.
Wilson, James Leroy, Children's Hospital, Boston.
Wilkinson, Robert Shaw, 12 Whittier Road, Wellesley.
Pallo, John, 24 Cross Street, Westfield.
Marlow, Frank William, Jr., 1284 Beacon Street, Brookline.
George, Henry Louis, Jr., 9 Primus Avenue, Boston.
Fish, James Ernest, Massachusetts General Hospital, Boston.
Howard, Philip J., Henry Ford Hospital, Detroit.
Whittier, Alice Agusta Skolfield, Hospital Cottages for Children, Baldwinsville.
Mackie, Thomas Turley, 103 E. 78th Street, New York City.
Freedman, Edward Philip, 11 Roxton Street, Dorchester.
Barr, Joseph Seaton, Massachusetts General Hospital, Boston.

NOTICE OF MEETING

PROGRAM INTERNATIONAL ASSEMBLY OF THE INTER-STATE POST-GRADUATE MEDICAL ASSOCIATION OF NORTH AMERICA

DETROIT, MICHIGAN, OCTOBER 21ST, 22ND, 23RD, 24TH, 25TH, 1929

MONDAY, OCTOBER 21ST

Diagnostic Clinic (Neurological).
Dr. Charles A. Elsberg, Professor of Neurological Surgery, Columbia University College of Physicians and Surgeons, New York, N. Y.
Diagnostic Clinic (Pediatric).
Dr. Herbert B. Wilcox, Professor of Diseases in Children, Columbia University College of Physicians and Surgeons, New York, N. Y.
Diagnostic Clinic (Surgical).
Dr. Charles H. Frazier, Professor of Surgery, University of Pennsylvania School of Medicine, Philadelphia, Pa.

Intermission

Diagnostic Clinic (Medical).
Dr. Leonard G. Rowntree, (Mayo Clinic), Professor of Medicine, University of Minnesota Graduate School of Medicine, Rochester, Minn.

OTO-LARYNGOLOGY

Address: "Some Problems in the Diagnosis and Treatment of Laryngeal Cancer."
Dr. Fielding O. Lewis, Professor of Laryngology, Jefferson Medical College, Philadelphia, Pa.
Address:
Dr. J. M. LeMée, Oto-Laryngologist of the Hôpital Necker, Hôpital des Enfants Malades and American Hospital of Paris, Paris, France.

Noon Intermission

Diagnostic Clinic (Surgery of the Hand).
Dr. Allen B. Kanavel, Professor of Surgery, Northwestern University Medical School, Chicago, Illinois.
Diagnostic Clinic (Pediatric).
Dr. W. McKim Marriott, Dean and Professor of Pediatrics, Washington University School of Medicine, St. Louis, Mo.
Diagnostic Clinic (Orthopedic).
Dr. William S. Baer, Clinical Professor of Orthopedic Surgery, Johns Hopkins University School of Medicine, Baltimore, Md.

Intermission

DISEASES OF THE HEART AND CIRCULATORY SYSTEM

Address: "Clinical and Pathological Observations on Coronary Diseases" (Lantern Demonstration).
Dr. Roy W. Scott, Professor of Clinical Medicine, Western Reserve University School of Medicine, Cleveland, Ohio.
Address: "Some Remarks About the Management of Aneurysm and Arteriovenous Fistula."
Dr. LeRoy Long, Dean and Professor of Surgery, University of Oklahoma School of Medicine, Oklahoma City, Okla.
Address: "Hyperpiesis and Hyperpiesia."
Dr. Thomas K. Monro, Regius Professor of Medicine, Medical Department University of Glasgow, Glasgow, Scotland.

Address:
Dr. Willis F. Manges, Clinical Professor of Roentgenology, Jefferson Medical College, Philadelphia, Pa.
Address: "Periodontal Disease in its Relation to General Pathological Conditions."
Sir Frank Colyer, K.B.E., F.R.C.S., Dental Surgeon, London, England.

Dinner Intermission

Address: "Treatment of Fractures."
Dr. William Darrach, Dean and Professor of Clinical Surgery, Columbia University College of Physicians and Surgeons, New York, N. Y.

NERVOUS SYSTEM

Address: "The Value of Ventriculography in the Diagnosis of Cerebellar Diseases."
Dr. Charles A. Elsberg, Professor of Neurological Surgery, Columbia University College of Physicians and Surgeons, New York, N. Y.
Address: "The Endocrine Relation of Certain Hereditary Disturbances of the Nervous System."
Dr. Walter Timme, Clinical Professor of Neurology, Columbia University College of Physicians and Surgeons, New York, N. Y.
Address: "The Mechanism and Treatment of Traumatic Epilepsy."
Dr. Wilder Penfield, Professor of Neurological Surgery, McGill University Faculty of Medicine, Montreal, Canada.
Address:
Dr. Charles H. Frazier, Professor of Surgery, University of Pennsylvania School of Medicine, Philadelphia, Pa.
Address: "Sympathectomy in Raynaud's Disease."
Dr. Allen B. Kanavel, Professor of Surgery, Northwestern University Medical School, Chicago, Illinois.

TUESDAY, OCTOBER 22ND

Diagnostic Clinic (Surgical).
Dr. William Darrach, Dean and Professor of Clinical Surgery, Columbia University College of Physicians and Surgeons, New York, N. Y.

Diagnostic Clinic (Dermatological).
Dr. Howard Fox, Professor of Dermatology and Syphilology, New York University, New York, N. Y.
Diagnostic Clinic (Surgical).
Dr. Carl A. Hamann, Professor of Applied Anatomy and Clinical Surgery, Western Reserve University School of Medicine, Cleveland, Ohio.

Intermission

Diagnostic Clinic (Medical).
Dr. Alan G. Brown, Professor of Medicine, University of Toronto Faculty of Medicine, Toronto, Canada.
Address: "The Importance to the Surgeon of an Understanding of Biochemistry."
Dr. William J. Mayo, Surgeon and Chief of Staff, Mayo Clinic, Rochester, Minn.
Address:
Professor E. F. Müller, Medical Department of the University of Hamburg, Hamburg, Germany.

Noon Intermission

Diagnostic Clinic (Surgical).
Dr. Arthur Dean Bevan, Clinical Professor of Surgery and Head of Surgical Department, Rush Medical College of the University of Chicago, Chicago, Illinois.
Diagnostic Clinic (Cardio-Vascular Renal Disease).
Dr. Elsworth S. Smith, Professor of Clinical Medicine, Washington University School of Medicine, St. Louis, Mo.
Diagnostic Clinic (Surgical).
Dr. William D. Haggard, Professor of Clinical Surgery, Vanderbilt University School of Medicine, Nashville, Tenn.

Intermission

NEOPLASMS

Address:
Dr. Joseph C. Bloodgood, Professor of Clinical Surgery, Johns Hopkins University School of Medicine, Baltimore, Md.
Address: "The Story of Tumors of the Breast from the Standpoint of the General Practitioner and Surgeon: Diagnosis, Treatment, Pathology and Prognosis."
Dr. Arthur Dean Bevan, Clinical Professor of Surgery and Head of Surgical Department, Rush Medical College of the University of Chicago, Chicago, Illinois.
Address: "Benign Tumors of the Breast."
Dr. Carl A. Hamann, Professor of Applied Anatomy and Clinical Surgery, Western Reserve University School of Medicine, Cleveland, Ohio.

DERMATOLOGY

Address: "Present Status of Roentgen Therapy of Diseases of the Skin."
Dr. James M. Martin, Professor of Roentgenology, Baylor University College of Medicine, Dallas, Texas.
Address: "Artificial Dermatitis Due to Plants, Medicaments, Irradiations and Malingering." (Lantern Demonstration).
Dr. Howard Fox, Professor of Dermatology and Syphilology, New York University, New York, N. Y.

Dinner Intermission

PEDIATRICS

Address: "Developmental Defects in Children—Structural, Functional and Mental."
Dr. Herbert B. Wilcox, Professor of Diseases in Children, Columbia University School of Medicine, New York, N. Y.
Address: "The Effects of Vomiting, Diarrhea and Water Loss on the Body and Newer Methods of Treatment."
Dr. W. McKim Marriott, Dean and Professor of Pediatrics, Washington University School of Medicine, St. Louis, Mo.
Address: "Prevention and Treatment of Scarlet Fever."
Dr. H. B. Cushing, Professor of Pediatrics, McGill University Faculty of Medicine, Montreal, Canada.
Address: "Infant Feeding with Special Reference to the Prevention of Rickets."
Dr. Alan G. Brown, Professor of Medicine, University of Toronto Faculty of Medicine, Toronto, Canada.

ARTHRITIS

Address: "Arthritis Deformans, Its Etiology and Treatment."
Dr. William S. Baer, Clinical Professor of Orthopedic Surgery, Johns Hopkins University School of Medicine, Baltimore, Md.
Address: "Some Recent Studies in Arthritis."
Dr. Leonard G. Rowntree, (Mayo Clinic), Professor of Medicine, University of Minnesota Graduate School of Medicine, Rochester, Minn.

WEDNESDAY, OCTOBER 23RD

Diagnostic Clinic (Surgical).
Dr. William E. Lower, Director, Cleveland Clinic Foundation; Associate Professor of Genito-Urinary Surgery, Western Reserve University School of Medicine, Cleveland, Ohio.
Diagnostic Clinic (Medical).
Dr. D. A. L. Graham, Professor of Medicine and Clinical Medicine, University of Toronto Faculty of Medicine, Toronto, Canada.
Diagnostic Clinic (Surgical).
Dr. John B. Deaver, Emeritus Professor of Surgery, University of Pennsylvania School of Medicine, Philadelphia, Pa.

Intermission

Diagnostic Clinic (Medical).
Dr. Harlow Brooks, Professor of Clinical Medicine, University and Bellevue Hospital Medical College, New York, N. Y.
Address:
Dr. Hugh Cabot, Dean and Professor of Surgery, University of Michigan Medical School, Ann Arbor, Michigan.
Address: "The Second Revolution in Ophthalmology." The Joseph Schneider Foundation Presentation.
Dr. George S. Derby, Professor of Ophthalmology, Harvard University Medical School, Boston, Mass.

Noon Intermission

Diagnostic Clinic (Surgical).
Dr. William S. Quinby, Clinical Professor of Genito-Urinary Surgery, Harvard University Medical School, Boston, Mass.

Diagnostic Clinic (Medical).
Dr. Elliott P. Joslin, Clinical Professor of Medicine, Harvard University Medical School, Boston, Mass.
Diagnostic Clinic (Surgical).
Dr. John M. T. Finney, Professor of Clinical Surgery, Johns Hopkins University School of Medicine, Baltimore, Md.

RESPIRATORY TRACT

Address: "Roentgenology of the Upper Respiratory Tract."
Dr. Henry K. Pancoast, Professor of Roentgenology, University of Pennsylvania School of Medicine, Philadelphia, Pa.
Address: "The Diagnosis of Pleural Effusions."
Dr. Arthur C. Christie, Professor of Roentgenology, George Washington University Medical School, Washington, D. C.

UROLOGY

Address: "The Surgical Treatment of Anomalies of the Genito-Urinary Tract."
Dr. William E. Lower, Director, Cleveland Clinic Foundation; Associate Professor of Genito-Urinary Surgery, Western Reserve University School of Medicine, Cleveland, Ohio.
Address:
Dr. William C. Quinby, Clinical Professor of Genito-Urinary Surgery, Harvard University Medical School, Boston, Mass.
Address: "The Diagnosis of Diabetes."
Dr. Elliott P. Joslin, Clinical Professor of Medicine, Harvard University Medical School, Boston, Mass.

Dinner Intermission

Address:
Dr. Harlow Brooks, Professor of Clinical Medicine, University and Bellevue Hospital Medical College, New York, N. Y.
Address: "Punching the Time-Clock of Age."
Dr. T. Wingate Todd, Professor of Anatomy, Western Reserve University School of Medicine, Cleveland, Ohio.
Address:
Dr. William D. Haggard, Professor of Clinical Surgery, Vanderbilt University School of Medicine, Nashville, Tenn
Address: "A Pen Picture of the Country Doctor."
Dr. R. F. Lischer, Vice President of the Southern Illinois Medical Society, Mascoutah, Illinois.

THURSDAY, OCTOBER 24TH

Diagnostic Clinic (Surgical).
Dr. John F. Erdmann, Professor of Surgery, New York Post Graduate Medical School, New York, N. Y.
Diagnostic Clinic (Gynecological).
Dr. Benjamin P. Watson, Professor of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, New York, N. Y.
Diagnostic Clinic (Surgical).
Dr. Alexander Primrose, Dean and Professor of Clinical Surgery, University of Toronto Faculty of Medicine, Toronto, Canada.

Intermission

Diagnostic Clinic (Medical).
Dr. Henry A. Christian, Professor of the Theory and Practice of Physic, Harvard University Medical School, Boston, Mass.
Diagnostic Clinic (Medical).
Dr. Campbell P. Howard, Professor of Medicine, McGill University Faculty of Medicine, Montreal, Canada.
Address:
Dr. T. de Martel, Surgeon, Hôpital de la Cite du Medi; Chief Surgeon, American Hospital, Paris, France.

Noon Intermission

Diagnostic Clinic (Surgical).
Dr. Dean Lewis, Professor of Surgery, Johns Hopkins University School of Medicine, Baltimore, Md.
Diagnostic Clinic (Medical).
Dr. David P. Barr, Professor of Medicine, Washington University School of Medicine, St. Louis, Mo.

OBSTETRICS AND GYNECOLOGY

Motion Picture: Caesarian Section.
Dr. Joseph B. DeLee, Professor of Obstetrics, Northwestern University Medical School, Chicago, Illinois.

Intermission

OBSTETRICS AND GYNECOLOGY (CONTINUED)

Address: "Is There a Place for the Trained Obstetric Nurse or Midwife in American Obstetrics?"
Dr. Benjamin P. Watson, Professor of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, New York, N. Y.
Address: "Contrasting Indications for Surgery and Radiation in the Treatment of Cancer of the Uterus."
Dr. John C. Polak, Professor of Obstetrics and Gynecology, Long Island College Hospital, Brooklyn, N. Y.

Address: "Varieties of Edema and Their Treatment."
Dr. Henry A. Christian, Professor of the Theory and Practice of Physic, Harvard Medical School, Boston, Mass.

THE ABDOMEN

Address: "Observations on Abdominal Pain."
Dr. Frederick J. Kalteyer, Associate Professor of Medicine, Jefferson Medical College of Philadelphia, Philadelphia, Pa.
Address: "Peritonitis."
Dr. John B. Deaver, Emeritus Professor of Surgery, University of Pennsylvania School of Medicine, Philadelphia, Pa.

Dinner Intermission

THE ABDOMEN (CONTINUED)

Address: "Post-Operative Abdominal Fistulae or Sinuses."
Dr. John F. Erdmann, Professor of Surgery, New York Post Graduate Medical School, New York, N. Y.
Address: "Intestinal Obstruction."
Dr. Alexander Primrose, Professor of Clinical Surgery, University of Toronto Faculty of Medicine, Toronto, Canada.
Address:
Dr. Rollin T. Woodyatt, Clinical Professor and Chairman of the Department of Medicine, Rush Medical College of the University of Chicago, Chicago, Illinois.

Address:
Dr. John M. T. Finney, Professor of Clinical Surgery, Johns Hopkins University School of Medicine, Baltimore, Md.

Address:
Dr. Dean Lewis, Professor of Surgery, Johns Hopkins University School of Medicine, Baltimore, Md.

Address:
Dr. Duncan A. L. Graham, Professor of Medicine, University of Toronto Faculty of Medicine, Toronto, Canada.

FRIDAY, OCTOBER 25TH

Diagnostic Clinic (Surgical).
Dr. Charles H. Mayo, Associate Chief of Staff, Mayo Clinic; Professor of Surgery, University of Minnesota Post-Graduate School of Medicine, Rochester, Minn.

Diagnostic Clinic (Surgical).
Dr. Frank H. Lahey, Director, Lahey Clinic, Boston, Mass.

Diagnostic Clinic (Medical).
Dr. Charles A. Elliott, Professor of Medicine, Northwestern University School of Medicine, Chicago, Illinois.

Diagnostic Clinic (Surgical).
Dr. Hugh Cabot, Dean and Professor of Surgery, University of Michigan, Medical School, Ann Arbor, Mich.

Diagnostic Clinic (Surgical).
Dr. George W. Crile, Director, Cleveland Clinic Foundation; Professor Emeritus of Surgery, Western Reserve University School of Medicine, Cleveland, Ohio.

Diagnostic Clinic (Surgical).
Dr. E. Starr Judd, Surgeon, Mayo Clinic, Rochester, Minn.

Noon Intermission

THE GALL-BLADDER AND LIVER

Address: "The Etiology of Gall-Bladder Infection."
Mr. David P. D. Wilkie, F.R.C.S., Professor of Surgery, Medical Department, University of Edinburgh, Edinburgh, Scotland.

Address: "The Newer Physiology of the Gall-Bladder."
Dr. A. C. Ivy, Professor of Physiology and Pharmacology, Northwestern University School of Medicine, Chicago, Illinois.

Address: "Cholecystitis."
Dr. E. Starr Judd, Surgeon, Mayo Clinic, Rochester, Minn.

Address: "Cirrhosis of the Liver."
Dr. Campbell P. Howard, Professor of Medicine, McGill University Faculty of Medicine, Montreal, Canada.

Address: "Practical Methods of Determination of Liver Function."
Dr. Charles A. Elliott, Professor of Medicine, Northwestern University School of Medicine, Chicago, Illinois.

Address:
Dr. Ferdinand Sauerbruch, Professor of Surgery and Head of the Department of Surgery, University of Berlin, Berlin, Germany.

Address:
Dr. Charles H. Mayo, Associate Chief of Staff, Mayo Clinic; Professor of Surgery, University of Minnesota Post Graduate School of Medicine, Rochester, Minn.

THE THYROID GLAND

Address: "End Results in Thyro-Cardiacs Three and a Half Years After Operation."
Dr. Frank H. Lahey, Director, Lahey Clinic, Boston, Mass.

Address: "The Pathology of Goiter."
Dr. Aldred S. Warthin, Professor of Pathology and Director of the Pathological Laboratory, University of Michigan School of Medicine, Ann Arbor, Michigan.

Address: "A Clinical Analysis of 20,000 Operations on the Thyroid Gland with Special Reference to the End Results."
Dr. George W. Crile, Director, Cleveland Clinic Foundation, Professor Emeritus of Surgery, Western Reserve University School of Medicine, Cleveland, Ohio.

BANQUET, FRIDAY EVENING, OCTOBER 25TH

Addresses by Distinguished Citizens of the World.

For other information address Dr. William B. Peck, Managing Director, Freeport, Illinois.

SOCIETY MEETINGS, CONGRESSES AND CONFERENCES

September 27-28—New England Surgical Society. Detailed notice appears on page 1227, issue of June 6.

October 7-19—New York Academy of Medicine. Detailed notice appears on page 468, issue of February 28.

October 13-18—General meeting of the International Society of Medical Hydrology and International League for Combating Rheumatism. Detailed notice appears on page 288, issue of August 8.

October 21, 22, 23, 24, 25—International Assembly of the Inter-State Post-Graduate Medical Association of North America. For detailed notice see page 341.

November 4, 5, 6 and 7, 1929—Clinical Congress and Eighth Annual Meeting of the American College of Physical Therapy. See page 149, issue of July 18, for details.

December 2-6—The Radiological Society of North America. Complete notice appears on page 149, issue of July 18.

May 5-10, 1930—First International Congress on Mental Hygiene. See page 191, issue of July 25, for details.

DISTRICT MEDICAL SOCIETY

Norfolk District Medical Society

Schedule of meetings for the year 1929-1930. Invitations have been sent to the speakers and the list is true only on condition of their acceptance.

October 29—Medfield State Hospital, Harding, Massachusetts. Papers by the Staff.

November 25—Roxbury Masonic Temple. Dr. Roger Graves, "Urology from the Standpoint of the General Practitioner." Surgical discussion. Medical discussion.

January 27, 1930—Roxbury Masonic Temple. "Recent Advances in Diagnosis and Treatment of Syphilis." Speaker to be announced.

February 24, 1930—Roxbury Masonic Temple, 8:00. Dr. Edwin H. Place has been invited to read a paper and has been given carte blanche in the selection of his subject.

March 24, 1930—Roxbury Masonic Temple. Dr. Burton E. Hamilton. Subject to be announced.

May 6, 1930—Annual Meeting. Program to be announced.

The Censors meet for the examination of candidates, November 7, 1929, and May 1, 1930, in the Roxbury Masonic Temple, 171 Warren Street, Roxbury, at 4:00 P. M. Applications must be in the hands of the Secretary at least one week previous to date of examination.

Owing to inability to engage the Roxbury Masonic Apartments on the last Tuesday of the month, such meetings as will be held in the Roxbury Temple will be held Monday evenings as per the dates above.

FRANK S. CRUICKSHANK,
Secretary, Norfolk District Medical Society.